09/139254

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DOCKET NO. PAT030188-US-NP

U.S. Patent No.: 6,291,523 B1

Inventor: Fujimoto, et al.

Assignee: Novartis AG

Issued: September 18, 2001

For: Certain 5-Alkyl-2-Arylaminophenylacetic Acids and Derivatives

Mail Stop Hatch-Waxman PTE
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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PATENT EXTENSION
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LETTER OF TRANSMITTAL OF APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir:

Transmitted herewith is an application for extension of patent term of United States Patent No. 6,291,523 B1 in accordance with 35 U.S.C. § 156. The original and 2 copies of the application are enclosed.

Each copy of this application includes the following:

--Letter of Transmittal of Application for Extension of Patent Term

--Application for Extension of Patent Term

--Exhibit A – Assignment of U.S. Pat. No. 6,291,523 B1

--Exhibit B – Approved Product Insert for Onsior®

--Exhibit C – FDA approval letter for Onsior®

--Exhibit D – U.S. Patent No. 6,291,523 B1

--Exhibit E – Maintenance Fee Statement for U.S. Pat. No. 6,291,523 B1

--Exhibit F – Approved FOI Summary for Onsior®

--Exhibit G – Cover Letter, Administrative NADA for Onsior®

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EB 907763642 US

The undersigned authorizes the Commissioner to charge Deposit Account No. 50-4389 in the amount of $1,120.00 for the fee pursuant to 37 C.F.R § 1.20(j)(1). The Commissioner is hereby authorized to charge any additional fees or credit any overpayment to the same account.

Respectfully submitted,

By: Todd L. Sladek

Date: 4/27/2011

Novartis Animal Health US, Inc.
3200 Northline Avenue, Suite 300
Greensboro, North Carolina 27408
Reg. No. 53,768
Tel: (336) 387-1601

09/139254

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DOCKET NO. PAT030188-US-NP

U.S. Patent No.: 6,291,523 B1

Inventor: Fujimoto, et al.

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Issued: September 18, 2001

For: Certain 5-Alkyl-2-Arylaminophenylacetic Acids and Derivatives

Mail Stop Hatch-Waxman PTE
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. § 156

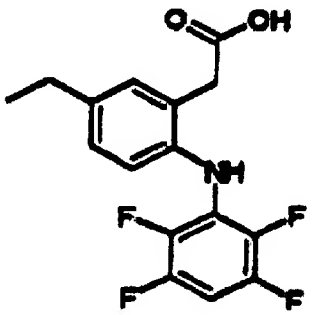
Dear Sir:

Applicant Novartis Animal Health US, Inc., which is an indirect, wholly-owned subsidiary of Novartis AG, the assignee of the entire interest in United States Patent No. 6,291,523 B1 (application serial number 09/139,254), by virtue of an assignment thereto, executed October 22, 1998 and recorded in the United States Patent and Trademark Office (USPTO) on April 26, 2001 (reel / frame number: 011752 / 0153) (**Exhibit A**) submits this Application for Extension of Patent Term under 35 U.S.C. § 156 and provides the following information in accordance with 37 C.F.R. § 1.710, et seq. The numbering of the following paragraphs corresponds to the numbering of the requirements for an application set forth in 37 C.F.R. § 1.740.

US Express Mail
EB 907763642 US

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure, or characteristics.

The approved product is Onsior® (robenacoxib), a new animal drug. The chemical name of the active ingredient of the approved product is [5-Ethyl-2-(2,3,5,6-tetrafluoro-phenylamino)-phenyl]-acetic acid. The generic name of the approved product is robenacoxib. The commercial name of the approved product is Onsior®. The structural formula of robenacoxib is:



The empirical formula is $C_{16}H_{13}F_4NO_2$. Robenacoxib is a selective inhibitor of cyclooxygenase-2 (COX-2) (see attached Approved Product Insert, **Exhibit B).**

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 512 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 360(b).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Onsior® was first approved by the FDA for commercial marketing for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration, in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age, for up to a maximum of 3 days on March 8, 2011. A copy of the FDA's approval letter is attached as **Exhibit C**.

(4) An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Onsior® is robenacoxib, as described in the attached Approved Product Insert (**Exhibit B**). Robenacoxib has not been previously approved for commercial marketing or use under the Food, Drug, and Cosmetic Act. The Administrative New Animal Drug Application (NADA) for Onsior® was approved on March 8, 2011 for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration, in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age, for up to a maximum of 3 days pursuant to Section 512 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 360(b).

(5) A statement that the application is being submitted within the 60-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing by FDA on March 8, 2011. The last day of the 60-day period on which this application could be submitted is May 7, 2011, which is a Saturday. As this submission is being made before May 7, 2011, it has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, date of issue, and the date of expiration.

Inventor:	Fujimoto, et al.
U.S. Patent No.:	6,291,523 B1
Date of Issue:	September 18, 2001
Date of Expiration:	September 18, 2018 (see below for explanation)

The U.S. patent application that matured into U.S. Patent No. 6,291,523 was filed August 25, 1998. Since this application was filed after June 8, 1995, the term of this patent is 20 years from the U.S. filing date of the earliest non-provisional application in the patent family. The application that matured into U.S. Patent No. 6,291,523 is the earliest non-provisional application filed in this family. Twenty years from the August 25, 1998 filing date is August 25, 2018. However, 24 days of patent term adjustment under 35 U.S.C. § 156(b) were awarded. Therefore, the expiry date of U.S. Patent No. 6,291,523 is September 18, 2018. No terminal disclaimers were filed in this case.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

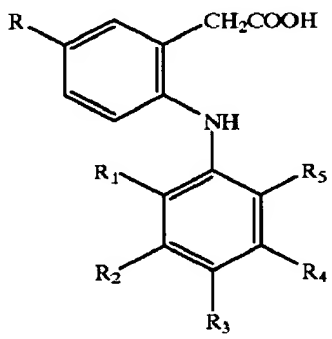
A copy of the patent, U.S. 6,291,523 B1, is attached as **Exhibit D**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

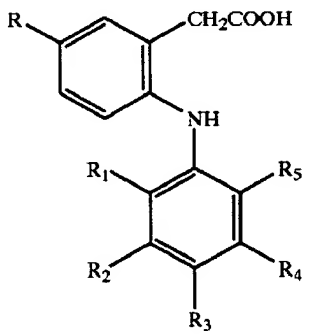
A copy of the receipt of the maintenance fee payment U.S. Patent No. 6,291,523 is attached as **Exhibit E**.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one applicable patent claim reads on the approved product or method of using or manufacturing the approved product.

U.S. Patent No. 6,291,523 B1 claims the active ingredient of the approved product and methods of using the same. Claims 17, 20, 22 and 25 claim methods of using the approved product. Claims 27, 30, 32 and 35 claim compositions containing the approved product. The following table demonstrates the manner in which claims 17, 20, 22, 25, 27, 30, 32 and 35 read on the approved product:

Claim	Demonstration
17. A method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cycloxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I (I)  wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy or ethoxy; R_4 is hydrogen or fluoro; R_5 is chloro, fluoro or trifluoromethyl; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.	In claim 17, when R is ethyl, R_1 is fluoro, R_2 is fluoro, R_3 is hydrogen, R_4 is fluoro and R_5 is fluoro, the claimed method encompasses treating pain and inflammation in cats using robenacoxib (the active ingredient in the approved product). The approved product has demonstrated selective cyclooxygenase-2 (COX-2) inhibition (robenacoxib inhibits cyclooxygenase-2 activity without substantially inhibiting cyclooxygenase-1 activity). Therefore, claim 17 reads on the approved method of use.

20. A method according to claim **17** wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen or ethoxy; R4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.	Claim 20 is dependent on claim 17 which encompasses the approved use of robenacoxib. Therefore, claim 20 reads on the approved product.
22. A method according to claim **17** wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2–R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.	Claim 22 is dependent on claim 17 which encompasses the approved use of robenacoxib. Therefore, claim 22 reads on the approved product.
25. A method according to claim **17** wherein the compound is 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid of formula I wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof.	Claim 25 is dependent on claim 17 which encompasses the approved use of robenacoxib. Therefore, claim 25 reads on the approved product.

27. A selective cyclooxygenase-2 inhibiting pharmaceutical composition substantially free of cyclooxygenase-1 inhibiting activity comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula **I** (I)  wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy or ethoxy; R_4 is hydrogen or fluoro; R_5 is chloro, fluoro or trifluoromethyl; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.	In claim 27, when R is ethyl, R_1 is fluoro, R_2 is fluoro, R_3 is hydrogen, R_4 is fluoro and R_5 is fluoro, the claimed compound is robenacoxib (the active ingredient in the approved product). The approved product has demonstrated selective COX-2 inhibition. The approved product is administered in combination with one or more pharmaceutically acceptable carriers (e.g., as a tablet). Therefore, claim 27 reads on the approved product.

30. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen or ethoxy; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.	Claim 30 depends on claim 27 which, when R is ethyl, R_1 is fluoro, R_2 is fluoro, R_3 is hydrogen, R_4 is fluoro and R_5 is fluoro, encompasses robenacoxib (the active ingredient in the approved product). The approved product has demonstrated selective COX-2 inhibition. The approved product is administered in combination with one or more pharmaceutically acceptable carriers (e.g., as a tablet). Therefore, claim 30 reads on the approved product.
32. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2–R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.	Claim 32 depends on claim 27 which, when R is ethyl, R_1 is fluoro, R_2 is fluoro, R_3 is hydrogen, R_4 is fluoro and R_5 is fluoro, encompasses robenacoxib (the active ingredient in the approved product). The approved product has demonstrated selective COX-2 inhibition. The approved product is administered in combination with one or more pharmaceutically acceptable carriers (e.g., as a tablet). Therefore, claim 32 reads on the approved product.
35. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid formula I wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; in combination with one or more pharmaceutically acceptable carriers.	Claim 35 depends on claim 27 which, when R is ethyl, R_1 is fluoro, R_2 is fluoro, R_3 is hydrogen, R_4 is fluoro and R_5 is fluoro, encompasses robenacoxib (the active ingredient in the approved product). The approved product has demonstrated selective COX-2 inhibition. The approved product is administered in combination with one or more pharmaceutically acceptable carriers (e.g., as a tablet). Therefore, claim 35 reads on the approved product.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(A) The exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective for the approved product on March 2, 2004, the date the Investigational New Animal Drug (INAD) was established by the FDA.

(B) The Administrative New Animal Drug Application (NADA) for the approved product was submitted on January 13, 2011 and was assigned NADA number 141-320 by the FDA.

(C) NADA 141-320 was approved on March 8, 2011.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The dates below indicate the start of the animal phase of each listed study. The data from all of these studies was submitted to and used by the FDA to approve the product. Indicated in parenthesis after each study identifier is the specific subject area the identified study supports. Although the specific study identifiers are not indicated therein, the results of the majority of these studies are discussed in the Freedom of Information (FOI) Summary for Onsior®. The approved FOI Summary is attached to this application as **Exhibit F**.

--September 15, 2003 – Study COXFRA(103) (Dosage characterization)
--May 24, 2005 – Study COX INT0104 (Dosage characterization)
--August 19, 2005 – Study CRA 05-088 (Safety)
--May 17, 2006 – Study CRA 06/054 (Dosage characterization)
--July 6, 2006 – Study CRA 04/094 (Dosage characterization)
--November 6, 2006 – Study NAH-06-0017 (Dosage characterization)
--December 2006 – Study CRA 07/137 (Dosage characterization)
--December 27, 2006 – Study NAH-06-0006 (Safety)
--October 2007 – Study CRA 08/124 (Dosage characterization)
--April 28, 2008 – Study NAH-07-0001 (Effectiveness and safety)
--May 1, 2008 – Study NAH-06-0007 (Safety)

In addition, the dates below are dates of approval letters from the FDA for the indicated technical sections of the Onsior® regulatory application. These dates reflect completed review by the FDA of the relevant technical section submitted by the applicant during the phased review process. These dates are also set forth

in the cover letter for applicant's administrative NADA application, a copy of which is attached as **Exhibit G**.

--September 25, 2009 – Target animal efficacy

--August 19, 2010 – Environmental impact

--October 13, 2010 – Target animal safety

--November 15, 2010 – Chemistry, manufacturing and controls

--December 20, 2010 – Final Freedom of Information Act summary

--December 23, 2010 – Labeling and approved facsimile labeling

--December 23, 2010 – All other information

(12) A statement beginning on a new page that, in the opinion of the applicant, the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

(A) Applicant Novartis Animal Health US, Inc. is of the opinion that U.S. Patent No. 6,291,523 B1 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for extension, as follows:

(i) 35 U.S.C. § 156(a): U.S. Patent No. 6,291,523 B1 claims active components and methods for using a composition having the characteristics of Onsior®.

(ii) 35 U.S.C. § 156(a)(1): The term of U.S. Patent No. 6,291,523 B1 has not expired before submission of this application.

(iii) 35 U.S.C. § 156(a)(2): The term of U.S. Patent No. 6,291,523 B1 has never been extended pursuant to 35 U.S.C. § 156.

(iv) 35 U.S.C. § 156(a)(3): This application is being submitted by the owner of record of the patent in accordance with the requirements of 35 U.S.C. § 156(d).

(v) 35 U.S.C. § 156(a)(4): The approved product has been subject to a regulatory review period before its commercial marketing or use.

(vi) 35 U.S.C. § 156(a)(5)(A): The commercial marketing or use of the approved product after the regulatory review period is the first permitted commercial marketing or use of the product under 21 U.S.C. 360(b), pertaining to new animal drugs.

(vii) 35 U.S.C. § 156(c)(4): No other patent has been extended for the same regulatory review period for any product.

(B) The length of extension claimed by applicant Novartis Animal Health US, Inc. is 835 days

(i) Pursuant to 37 C.F.R § 1.778(c), the regulatory review period under 35 U.S.C. § 156(g)(4)(B) began on March 2, 2004. The regulatory review period ended on March 8, 2011. U.S. Patent No. 6,291,523 B1 issued on September 18, 2001, prior to the date the regulatory review period began.

(a) Under 35 U.S.C. § 156(c), patent term shall be extended by the time equal to the regulatory review period that occurs after the date the patent is issued. Therefore, the applicable "testing phase" under 37 C.F.R § 1.778(c)(1) began on March 2, 2004 (INAD date) and ended on January 13, 2011 (NADA submission). This is a period of 2,508 days.

(b) The applicable "approval phase" under 37 C.F.R. § 1.778(c)(2), began on January 13, 2011 and ended on March 8, 2011. This is a period of 54 days.

(ii) Pursuant to 37 C.F.R § 1.778(a), (c)(1) and (c)(2), the claimed patent term extension is one half of the above 2,508 days (1254 days) plus the above 54 days. The total is 1308 days. Accordingly, 1308 days of patent term extension are requested. Addition of 1308 days to the original September 18, 2018 expiration date of U.S. 6,291,523 B1 results in an expiration date of April 18, 2022.

(iii) Under 35 U.S.C. § 156(g)(6)(A), the length of the patent extension may not exceed 5 years. Addition of 5 years to the original September 18, 2018

expiration date of U.S. 6,291,523 B1 is September 18, 2023. Since April 18, 2022, calculated in the paragraph immediately above, is earlier than September 18, 2023, the length of the patent extension does not exceed 5 years.

(iv) Under 35 U.S.C. § 156(c)(3), the period between the approval date for the approved product (March 8, 2011) and the expiration date of the relevant patent, based on the calculated term extension (April 18, 2022 for U.S. 6,291,523 B1), cannot exceed 14 years. The calculated period between March 8, 2011 and April 18, 2022, is 11 years, 1 month, 10 days, which does not exceed 14 years. March 8, 2011 plus 14 years is March 8, 2025.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension.

The undersigned hereby authorizes the Commissioner to deduct the $1,120.00 fee (1.20(j)(1)), along with any other fees that may be due with this submission, from Deposit Account No. 50-4389.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed is set forth below.

Leslie Fischer
Novartis Pharmaceuticals Corporation
One Health Plaza, Building 104
East Hanover, New Jersey 07936
Tel: (862) 778-9308

(16) This application is accompanied by two additional copies (for a total of three copies).

Respectfully submitted,

By: Leslie Fischer

Date: 4/26/11

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 104
East Hanover, New Jersey 07936
Reg. No. 58,393

By: Todd L. Sladek

Date: 4/27/2011

Novartis Animal Health US, Inc.
3200 Northline Avenue, Suite 300
Greensboro, North Carolina 27408
Reg. No. 53,768

Both registered practitioners on behalf of the patent owner

Exhibits

A: Assignment of U.S. Pat. No. 6,291,523 B1 from the inventors to Novartis AG
B: Approved Product Insert for Onsior®
C: FDA approval letter for Onsior®
D: U.S. Patent No. 6,291,523 B1
E: Maintenance Fee Statement for U.S. Pat. No. 6,291,523 B1
F: Approved FOI Summary for Onsior®
G: Cover Letter, Administrative NADA for Onsior®

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6291523 **Issue Dt:** 09/18/2001 **Application #:** 09139254 **Filing Dt:** 08/25/1998

Inventors: ROGER A. FUJIMOTO, LESLIE W. MCQUIRE, BENJAMIN B. MUGRAGE, JOHN H. VAN DUZER

Title: CERTAIN 5-ALKYL-2-ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES

Assignment: 1

Reel/Frame: 011752/0153 **Recorded:** 04/26/2001 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:	FUJIMOTO, ROGER A.	**Exec Dt:** 10/22/1998
	MCQUIRE, LESLIE W.	**Exec Dt:** 10/22/1998
	MUGRAGE, BENJAMIN B.	**Exec Dt:** 10/22/1998
	VAN DUZER, JOHN H.	**Exec Dt:** 10/22/1998
	XU, DAQIANG	**Exec Dt:** 10/23/1998

Assignee: NOVARTIS AG
SCHWARZWALDALLEE 215
BASEL, SWITZERLAND 4058

Correspondent: NOVARTIS CORPORATION
THOMAS HOXIE
PATENT AND TRADEMARK DEPT.
564 MORRIS AVENUE
SUMMIT, NJ 07901-1027

Search Results as of: 04/21/2011 02:03 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.1

Web interface last modified: Apr 30, 2009 v.2.1

US Express Mail EB907763642 US

Exhibit B - Product Insert

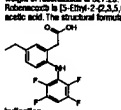
Product	Onsior Cat 6mg	Pack Size	3x10 CRB	GMR	012999	Mat-No	600837
Format	180 x 589 mm	Ektrasat		PP	Country		USA
Colors				Black	Duo-Size 100%	Print-Size	89%
Contact	Barbara Hartmann	Agency		Schwarz	Program	Adobe InDesign CS4	
ARTWORK SPECIFICATION					Version	2	Date 14.01.2011

onsior®
(robenacoxib)
6 mg Tablets for Cats

For Oral Use In Cats Only

Caution:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
ONSIOR (robenacoxib) is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID) of the coxib class. Tablets are round, beige to brown in color, not scored, flavored and contain 6 mg robenacoxib. The molecular weight of robenacoxib is 377.28. The empirical formula is $C_{19}H_{19}F_2NO_5$. Robenacoxib is [3-Ethyl-2-(2,3,5,6-tetradeuoro-phenylamino)-phenyl]-acetic acid. The structural formula is:



Indication:
ONSIOR tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration, in cats ≥ 5.5 lbs (2.5 kg) and ≥ 6 months of age, for up to a maximum of 3 days.

Dosage and Administration:
Always provide "Information for Cat Owners" Sheet with prescription. Carefully consider the potential benefits and risk of ONSIOR tablets and other treatment options before deciding to use ONSIOR tablets. Use the lowest effective dose for the shortest duration consistent with individual response.

The dose of ONSIOR tablets is 0.45 mg/lb (1 mg/kg) orally once daily, for a maximum of three days. See dosing chart for dosage directions.

Dosage Directions: For oral use in cats ≥ 5.5 lbs and ≥ 6 months of age, for up to a maximum of 3 days. Tablets are not scored and should not be broken.

Body weight	6 mg ONSIOR (robenacoxib) Tablet
5.5 to 13.2 lbs (2.5 to 6 kg)	1 whole tablet once daily
13.3 to 26.4 lbs (6.1 to 12 kg)	2 whole tablets once daily

The first dose should be administered approximately 30 minutes prior to surgery, at the same time as the pre-anesthetic agents are given. ONSIOR tablets may be given with or without food.

If a second and third dose is dispensed to the client to administer at home, doses should be dispensed in the dispensing envelope with the attached information for Owner Sheet intact. Do not remove information for Cat Owner Sheet. Record when the first dose was administered on the dispensing envelope. Cats weighing ≥ 13.3 lbs may require two blister cards, each dispensed in an individual dispensing envelope.

Contraindications:
ONSIOR tablets should not be used in cats that have a hypersensitivity to robenacoxib or known intolerance to NSAIDs.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.
For use in cats only.

All cats should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data prior to administration of an NSAID.
Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given an "Information for Cat Owners" Sheet about ONSIOR tablets.

Do not administer ONSIOR tablets in conjunction with any other oral or injectable NSAID or corticosteroid.

Precautions:
Appetite should be monitored in cats receiving ONSIOR tablets.

Stop administration of ONSIOR tablets if appetite decreases.

The use of ONSIOR tablets has not been evaluated in cats younger than 6 months of age, cats weighing less than 5.5 lbs, cats used for breeding, or in pregnant or lactating cats.

The use of ONSIOR tablets in cats with cardiac disease has not been studied. ONSIOR tablets has been shown to prolong the QT interval in a laboratory setting.

As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Cats that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Anesthetic drugs may affect renal perfusion; approach concomitant use of anesthetics and NSAIDs cautiously. Appropriate monitoring procedures (including ECG) should be employed during all surgical procedures. The use of parenteral fluids during surgery is recommended to decrease potential renal complications when using NSAIDs perioperatively.

If additional pain medication is needed after a daily dose of ONSIOR tablets, a non-NSAID/non-corticosteroid class of analgesic may be necessary. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit prostaglandins which maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforations. Do not use ONSIOR tablets concomitantly with other anti-inflammatory drugs, such as NSAIDs or corticosteroids. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

The use of concomitantly protein-bound drugs with ONSIOR tablets has not been studied in cats. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of ONSIOR tablets has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. Concurrent medications used during the field study with ONSIOR tablets included antiparasiticides, anesthetics, pre-anesthetic medications, and antibiotics.

The effect of cyclo-oxygenase inhibition and the potential for thromboembolic occurrence or a hypercoagulable state has not been evaluated. It is unknown whether cats with a history of hypersensitivity to ß lactam drugs will exhibit hypersensitivity to ONSIOR tablets. Robenacoxib is poorly soluble in water and in acid solutions readily degrades to form γ-lactam. In cats, lactam is a metabolite of robenacoxib. Additionally, lactam is a degradation product that increases over the shelf-life of the tablets. Neurologic signs have been associated with the use of ß lactam drugs; it is unknown if the lactam in robenacoxib may cause similar neurologic signs (**See Animal Safety**). Robenacoxib may prolong the QT interval; the associated risk of developing ventricular arrhythmia is unknown. The use of robenacoxib with other drugs shown to prolong the QT interval is not recommended. Commonly used drugs that prolong the QT interval include antihistamines and prokinetic drugs.

Adverse Reactions:
In a controlled field study, a total of 249 male and female cats representing 8 breeds, 6 months to 13 years old, weighing 5.5 – 15 lbs were included in the field safety analysis. The following table shows the number of cats exhibiting each observation.

Adverse Reactions in the Postoperative Pain Field Study[1]

Clinical Sign	ONSIOR 6 mg Tablets for Cats (robenacoxib) n = 167	Placebo (vehicle control) n = 82
Inappetance, weight loss	4	2
Incision site bleeding	7	1
Incision site infection	6	2
Decreased activity, lethargy	4	1
Cystitis, hematuria	3	0
Hair loss, excoriation, bruising	2	0
Vomiting	4	1
Hematochezia, diarrhea	3	1
Respiratory, cardiac arrest	1	0
Incoordination, weakness	1	1
Death	0	1

[1]Cats may have experienced more than one of these signs during the study.

The most commonly reported adverse reactions were surgical site bleeding, infected surgery sites, lethargy, vomiting and inappetance. Changes in the clinical pathology values were not considered clinically significant.

To report suspected adverse drug events, contact Novartis Animal Health at 1-800-332-2761 or the FDA at 1-800-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm. For technical assistance, contact Novartis Animal Health at 1-800-332-2761.

Information for Cat Owners:
ONSIOR tablets, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance.

Adverse reactions may include vomiting, diarrhea, decreased appetite, dark or tarry stools, increased water consumption, increased urination, anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Warnings and Adverse Reactions). Owners should be advised to discontinue ONSIOR tablets and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated.

Clinical Pharmacology:
In an inflammation model in cats, robenacoxib had analgesic, anti-inflammatory and anti- pyretic actions with a rapid onset of action (0.5 h).[1] In an *in vitro* whole blood assay in cats, robenacoxib demonstrated selective COX-2 inhibition.[2] The clinical relevance of this data has not been shown. Robenacoxib is an analog of diclofenac.

Absorption
After oral administration of robenacoxib tablets at 1 mg/kg without food, peak blood concentrations are attained rapidly with a median T_{max} of 0.5 h, a mean C_{max} of 1158 ng/ml and a mean AUC of 1337 ng.h/ml. Co-administration of robenacoxib tablets with one third of the daily food ration produced no change in median T_{max} (0.5 h), mean C_{max} (1201 ng/ml) or mean AUC (1383 ng.h/ml). Co-administration of robenacoxib tablets with the entire daily food ration produced no delay in median T_{max} (0.5 h), but a lower mean C_{max} (691 ng/ml) and a lower mean AUC (1063 ng.h/ml). The systemic mean bioavailability of robenacoxib tablets was 49% without food. The pharmacokinetics of robenacoxib does not differ between male and female cats.

Distribution
Robenacoxib has a relatively small volume of distribution (mean Vss = 190 ml/kg) and is highly bound to plasma proteins (>99%). Robenacoxib persists longer in the inflammatory exudate of a tissue cage model than in blood. The median robenacoxib elimination half-life in exudate was about 27 hours versus 2.5 hours for blood.

Biotransformation
Robenacoxib is extensively metabolized by the liver in cats. The systemic exposure of lactam metabolite is about 25% of robenacoxib exposure following oral administration to fed cats. Further, the systemic exposure to lactam appears to be two-fold greater in fed cats than fasted cats. Apart from one lactam metabolite, the identity of other metabolites is not known in cats.

Elimination
Robenacoxib is rapidly cleared from blood (mean clearance (Cl$_B$) = 0.44 L/kg/h) with an elimination mean half-life ($t_{1/2}$) of 1.1 hours after intravenous administration. After oral administration of tablets, the terminal mean $t_{1/2}$ from blood was 1.7 hours, and elimination occurs predominantly through the biliary route (fecal and urinary excretion are 60 and 16.5% respectively).

Animal Safety:
21 Day Target Animal Safety Study: In a 21-day laboratory tolerance study, 8 month-old healthy, DSH cats (4/sex/group) were administered robenacoxib at a dose of 0 mg/kg or 24 mg/kg/day (10X the maximum exposure based on the single, 6 mg tablet size). All cats survived to study termination. Vomiting and decreased activity was noted in some of the treated cats. Two cats in the 10X group exhibited abnormal rear limb neurologic function. One of these cats also exhibited a head tilt and nystagmus at the end of the study. Mean food consumption was less in the 10X group. The mean kidney weights were lower in the 10X group compared to the control group; and the mean thymus weights were also lower in the 10X group compared to the controls. Two cats in the 10X group had chronic interstitial nephritis on histopathology. One 10X cat had a focal cecal/large intestinal erosion. One 10X cat and one control cat had periportal, multifocal necrosis in one lobe of the liver. There were four 10X cats and 2 control cats with renal tubular degeneration. Under the conditions of this study, robenacoxib was well tolerated when administered at 24 mg/kg/day for 21 days, except for 2 cats in the 10X group with neurologic signs.

42 Day Target Animal Safety Study: In a 42 day study, 8 month-old, healthy cats were administered robenacoxib at 0, 2, 6 or 10 mg/kg/twice daily. Small thymuses were noted in all robenacoxib-treated groups with corresponding organ weight decreases and/or atrophic changes on histopathology. There was a decrease in the kidney weights in the 10 mg/kg/twice daily-group compared to the controls. Vomiting was the most common adverse reaction noted in the treated cats. An adequate safety margin was demonstrated for ONSIOR tablets when administered under the conditions of this 42-day study.

6 Month Target Animal Safety Study: In a 6 month study, 8 month-old, healthy cats (4/sex/group) were administered robenacoxib at 0, 1X (2.4 mg/kg), 3X (7.2 mg/kg) or 5X (12 mg/kg) once daily. One 5X cat had clonic seizures on Day 115 and was atonic on Day 175. One 5X cat had skin cold to the touch on Day 106. One cat in the 1X group experienced urethral obstruction/FLUTD. Vomiting, decreased activity, injected sclera and soft stools were the most common adverse reactions observed in the treated groups. Soft stools and injected sclera were also observed in the control group.

The mean body weights in the 1X and 3X groups were lower than the controls from Day 21 – Day 182; and lower in the 5X group from Day 28 – Day 182. There was a clear dose-related and possibly time-related increase in the QTc interval at Day 41 and Day 175, particularly in the 3X and 5X groups, no other ECG abnormalities were noted.

There was no obvious accumulation in C_{max} or AUC between Days 1, 31 and 171, and there was no apparent difference in parameters between males and females. The following parameters were calculated for the 1X dosage: T_{max} was 0.5 h (median), the dose-normalized mean C_{max} was 668 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 902 h*ng/mL. Similarly, the following parameters were calculated for the 3X dosage: T_{max} was 0.5 h (median), the dose-normalized mean C_{max} was 1019 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1394 h*ng/mL. For the 5X dosage the following parameters were calculated: T_{max} was 1.0 h (median), the dose-normalized mean C_{max} was 1198 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1884 h*ng/mL. A post hoc analysis of PK parameters revealed that dose normalized C_{max} and AUC were greater than dose proportional.

The mean kidney weights were lower in all robenacoxib-treated groups. One 5X cat with decreased kidney weight and size also had transient increases in BUN and creatinine. There were transient increases in AST, amylase, and ALT in the 3X and 5X cats from Day 30 – Day 183. There was an increased severity of the tubular degeneration/hypertrophy in the kidneys of two 1X and two 5X cats with inflammation, papillary necrosis and papillary mineralization.

An increased incidence of minimal to mild Kupffer cell pigmentation was observed in the livers of all robenacoxib-treated cats; however, no hepatocellular damage was noted on histopathology. One cat had a focal, minimal ulcer of the gastric fundus (peptic and parietal cells).

This 6 month safety study supports the safe use of ONSIOR tablets for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats for a maximum of 3 days.

Effectiveness:
Effectiveness was demonstrated using ONSIOR tablets in a masked, placebo-controlled, multi-site field study involving client-owned cats. In this study, 249 cats presenting for ovariohysterectomy or castration in conjunction with an orthopedic procedure only) were randomly administered ONSIOR tablets or a placebo. Drug was administered approximately 30 minutes prior to surgery along with pre-anesthetic medications and continued once daily for two additional treatments. Effectiveness was evaluated in 244 cats and field safety was evaluated in 249 cats. A statistically significant difference in the proportion of treatment successes in the ONSIOR tablets treatment group (137/164 or 83.5%) compared to the placebo, vehicle control group (43/80 or 53.8%) was observed. Twenty-seven out of 164 robenacoxib cases (16.5%) and 37 out of 80 placebo cases (46.2%) were treatment failures. Statistically significant differences for pain elicited on palpation at the spay or castration incision site, behavior following social interaction and posture score at various post-surgical time points were also observed. The results of the field study demonstrate that ONSIOR tablets, when administered for a maximum of three days, are effective and well-tolerated for the control of postoperative pain associated with onychectomy, ovariohysterectomy and castration in cats.

How Supplied:
ONSIOR tablets are available as 6 mg round flavored tablets in blisters and are supplied in blister cards containing 3 tablets. The blister cards are supplied in a veterinary carton containing 10 blister cards and are to be dispensed 1 card per patient in an ONSIOR tablets dispensing envelope containing veterinary insert and owner information sheet, supplied with the product.

Storage Conditions:
Store at controlled room temperature, between 59° and 77°F (15-25°C).

Manufactured for: Novartis Animal Health US, Inc.
Greensboro, NC 27408 USA

References:
[1]Giraudel, J.M., King, J.N., Jeunesse, E.C., Lees, P. & Toutain, P.L. (2008). Use of a pharmacokinetic/pharmacodynamic approach in the cat to determine a dosage regimen for the COX-2 selective drug robenacoxib. *J Vet Pharmacol Ther* 2009;32:19-30.
[2]Giraudel, J.M., Toutain, P.L., King, J.N., & Lees, P. Differential inhibition of cyclooxygenase isoenzymes in the cat by the COX-2 selective drug robenacoxib. *J Vet Pharmacol Ther* 2009;32:31-40.

NADA # 141-320, Approved by FDA

NAHONS-PET/6mg/MPI/1

US Express Mail
EB 907763642 US

NOVARTIS
ANIMAL HEALTH

NOVARTIS

Product	Onsior Cat 6mg	Pack Size	3x10 TAB	CMR	012980	Mat-Nr	600697
Format	180 x 540 mm	Element	FP	Country		USA	
Colors			Black	Doc-Size 100%		Print-Size	99%
Contact	Barbara Martineau	Agency	Inhouse	Program		Adobe InDesign CS4	
ARTWORK SPECIFICATION				Version	5	Date	14.01.2011

onsior®
(robenacoxib)
6 mg Tablets for Cats

For Oral Use In Cats Only

Information for Cat Owners – You should read this information before starting your cat on ONSIOR tablets.

What is ONSIOR?
ONSIOR (robenacoxib) tablets are a prescription non-narcotic, non-steroidal anti-inflammatory (NSAID) of the coxib class. ONSIOR (robenacoxib) tablets are for the control of postoperative pain and inflammation associated with orthopedic surgery (declaw), ovariohysterectomy (spay) and castration (neuter) in cats greater than or equal to 5.5 pounds (2.5 kg) and greater than or equal to 6 months of age; for a maximum of 3 days.

Your cat received the first dose of ONSIOR tablets in the hospital prior to surgery, which should be noted on the dispensing envelope you received. Your cat may be given ONSIOR tablets once every 24 hours, for two additional doses (a maximum of 3 doses). Follow the instructions given to you by your veterinarian.

This summary contains important information about ONSIOR tablets but does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about ONSIOR tablets for cats.

What kind of results can I expect when my cat takes ONSIOR tablets for postoperative pain and inflammation?
ONSIOR tablets may help your cat to recover more comfortably by controlling postoperative pain and inflammation following orthopedic (declaw), ovariohysterectomy (spay), or castration surgery (neuter).
- Control of postoperative pain and inflammation may vary from cat to cat.
- Administer ONSIOR tablets according to your veterinarian's directions, for a maximum of 3 days.
- Consult your veterinarian if your cat appears to be uncomfortable.

What cats should not take ONSIOR tablets?
Your cat should not be given ONSIOR tablets if s/he:
- Has had an allergic reaction to robenacoxib, the active ingredient in ONSIOR 6 mg tablets for cats
- Has had an allergic reaction (such as hives, facial swelling, or red or itchy skin) to aspirin or other NSAIDs
- Is less than 5.5 lbs or less than 6 months of age
- Has a loss of appetite/decreased appetite
- Has bloody stool or vomit
- Is presently taking aspirin, other NSAIDs, or corticosteroids
- Has a pre-existing kidney or liver condition
- Has any condition predisposing to dehydration

ONSIOR tablets should only be given to cats.
People should not take ONSIOR tablets. Keep ONSIOR tablets and all medication out of reach of children. Call your physician immediately if you accidentally take ONSIOR tablets.

Tell your veterinarian about:
- Any side effects your cat has previously experienced from ONSIOR tablets or other NSAIDs
- Any digestive upset (vomiting or diarrhea) your cat has had
- Any cardiovascular, kidney or liver disease your cat has had
- Any other medical problems or allergies that your cat has now or has had in the past
- All medications that you are giving your cat or plan to give your cat, including those you can get without prescription and any dietary supplements
- If you plan to breed your cat, or if your cat is pregnant or nursing

Talk to your veterinarian about:
- The surgery procedure performed on your cat
- What tests were done before surgery and prior to administering ONSIOR tablets
- The signs of postoperative pain or inflammation that may occur following surgery
- Normal events that can be expected after your cat undergoes surgery
- How often your cat may need to be examined by your veterinarian
- The risks and benefits of using ONSIOR tablets

How to give ONSIOR tablets to your cat.
ONSIOR tablets should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of ONSIOR tablets is right for your cat. ONSIOR tablets should only be given once a day and for no longer than 3 days. ONSIOR tablets should not be broken. ONSIOR tablets should be given by mouth and may be given with or without food.

What are the possible side effects that may occur in my cat during therapy with ONSIOR tablets?
ONSIOR tablets may cause some side effects in individual cats. These are normally mild, but serious side effects have been reported in cats taking non-steroidal anti-inflammatory drugs (NSAIDs) including ONSIOR tablets. Serious side effects can result in death. It is important to stop the medication and contact your veterinarian immediately if you think your cat may have a medical problem or side effect while on ONSIOR tablets. If you have additional questions about possible side effects, talk with your veterinarian or call Novartis Animal Health at 1-800-332-2761.

Look for the possible following side effects that may indicate that your cat is having a problem:
- Decrease in appetite
- Vomiting
- Change in bowel movements such as diarrhea or change in stool color
- Change in drinking or urination
- Change in behavior, such as depression or restlessness

If any of the above signs are noticed in your cat, stop administering ONSIOR tablets and call your veterinarian.

Can ONSIOR tablets be given with other medications?
ONSIOR tablets should not be given with other non-steroidal anti-inflammatory drugs (NSAIDs - i.e. aspirin, meloxicam) or corticosteroids (i.e. prednisone).

Always tell your veterinarian about all medications that you have given your cat in the past, and any medications that you are planning to give with ONSIOR tablets.

What can I do in case my cat eats more than the prescribed amount of ONSIOR tablets?
Contact your veterinarian immediately if your cat eats more than the prescribed amount of ONSIOR tablets.

What else should I know about ONSIOR tablets?
This sheet provides a summary of information about ONSIOR tablets. If you have any questions or concerns about ONSIOR tablets or postoperative pain and inflammation, talk to your veterinarian.

As with all prescribed medications, ONSIOR tablets should only be given to the cat for which they are prescribed. They should be given to your cat only for the condition for which they were prescribed, at the prescribed dose, as directed by your veterinarian.

NADA 141-320, Approved by FDA

NOVARTIS
ANIMAL HEALTH

Exhibit C - FDA Approval

NADA 141-320-A-0000-OT
APPROVAL DATE: March 8, 2011
CVM#201094

FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

FACSIMILE TRANSMISSION

DATE: March 9, 2010	TIME: 5:35 p.m.
TO: Novartis Animal Health US, Inc. Attention: Elizabeth D. Norton, D.V.M. Senior Regulatory Affairs Manager 3200 Northline Ave., suite 300 Greensboro, NC 27408	FROM: ☐ Dr. Mary Allen ☐ Dr. Mohammad Sharar ☐ Ms. Bonnie Bodo ☒ Dr. Robin Keyser OFFICE OF NEW ANIMAL DRUG EVALUATION HFV-107
TEL. 336-387-1009	DHHS/FDA/CVM/ONADE/HFV-107 TEL. ☐ (240) 276-8128 ☐ (240) 276-9179 ☐ (240) 276-8198 ☒ (240) 276-8130
FAX: 336-387-1168	METRO PARK NORTH II 7500 STANDISH PLACE ROCKVILLE, MD 20855

Number of pages (including cover sheet): __3__

CVM/ONADE FAX NUMBER: (240) 276-8242

US Express Mail / EB 907763642 US

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR - 8 2011

N-141320-A-0000-OT

Novartis Animal Health US, Inc.
Attention: Elizabeth D. Norton, D.V.M.
Senior Regulatory Affairs Manager
3200 Northline Ave., suite 300
Greensboro, NC 27408

Re: Request for original approval of ONSIOR

Dear Dr. Norton:

We approve your original new animal drug application (NADA) for ONSIOR dated January 13, 2011, and amended on January 31, 2011 (M-0001) under section 512(c)(1) of the Federal Food, Drug, and Cosmetic Act (the act). ONSIOR (robenacoxib) tablets are approved for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats $\geq$ 5.5 lbs (2.5 kg) and $\geq$ 6 months of age; for up to a maximum of 3 days. The expiration dating for this new animal drug is 48 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this approval according to 21 CFR 514.8. Any change to the conditions of the approval may require the submission of a supplemental application.

ONSIOR, as approved in this letter, qualifies for FIVE years of marketing exclusivity under section 512(c)(2)(F)(i) of the act beginning as of the date of this letter because no active ingredient of the new animal drug has previously been approved.

Your final printed labeling must be identical to the approved labeling submitted January 31, 2011 (N-141320-M-0001, package inserts, client information sheets, blister pack, dispensing envelope, and carton). Please submit in triplicate three paper copies (a total of nine copies) of each component of the final printed labeling before distributing and marketing your new animal drug. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

Under current good manufacturing practice (cGMP) regulations (21 CFR 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation

information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the act.

If you submit correspondence relating to this approval, your correspondence should reference the date and the principal submission identifier found at the top of this letter. If you have any questions or comments, contact Dr. John M. Mussman, Acting Director, Division of Therapeutic Drugs for Non-Food Animals, at 240-276-8354.

Sincerely,

Bernadette Dunham

Bernadette Dunham, D.V.M., Ph.D.
Director
Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary

Exhibit D

US006291523B1

(12) **United States Patent**
Fujimoto et al.

(10) **Patent No.: US 6,291,523 B1**
(45) **Date of Patent: Sep. 18, 2001**

(54) **CERTAIN 5-ALKYL-2-ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES**

(75) Inventors: **Roger A. Fujimoto**, Morristown; **Leslie W. McQuire**, Warren; **Benjamin B. Mugrage**, Basking Ridge; **John H. van Duzer**, Asbury; **Daqiang Xu**, Whippany, all of NJ (US)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 24 days.

(21) Appl. No.: **09/139,254**

(22) Filed: **Aug. 25, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/069,837, filed on Aug. 28, 1997, and provisional application No. 60/057,803, filed on Aug. 28, 1997.

(51) **Int. Cl.**[7] **A61K 31/216**; C07C 229/42

(52) **U.S. Cl.** **514/533**; 514/567; 560/45; 560/47; 560/48

(58) **Field of Search** 514/533, 567; 560/45, 47, 48

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,531,493	9/1970	Gittos et al. .
3,558,690	1/1971	Sallmann et al. .
3,652,762	3/1972	Sallmann et al. .
3,895,063	7/1975	Sallmann et al. .
4,173,577	11/1979	Sallmann et al. .
4,548,952	10/1985	Casas .
5,958,978	9/1999	Yamazaki et al. .

FOREIGN PATENT DOCUMENTS

3445011	6/1985	(DE) .
3445011 A1	6/1985	(DE) .
865788 A1	9/1998	(EP) .
WO 94/04484	3/1994	(WO) .
WO 96/00716	1/1996	(WO) .
WO 97/09977	3/1997	(WO) .

OTHER PUBLICATIONS

Chemical Abstract 118: 80787 (1993).
Chemical Abstracts 104: 109230 (Abstract of DE 3445011).
Griswold et al., Medicinal Research Reviews, vol. 16, No. 2, pp. 181–206 (1996).
Moser et al., J. Med. Chem., vol. 33, pp. 2358–2368 (1990).
Sircar J.C., Curr.Opin.Invest.Drugs, vol. 2 (4), pp. 403–407 (1993).
Englehardt G., Z. Rheumatol, vol. 53, Suppl. 1, p. 68 (1994).
Englehardt G., Eur. J., Clin. Pharmacology, vol. 47 (No. 1) p. A98 (1994).
Brit. J. Pharmacol., vol. 112, Proc. Suppl., p. 183P (1994).
Klein T. et al., Biochemical Pharmacology, vol. 48, No. 8, pp 1605–1610 (1994).
Mitchell J.A. et al., Proc.Natl.Acad.Sci.USA, vol. 90, pp. 11693–11697 (1994).
Pallapies D. et al., Life Sciences, vol. 57, No. 2, pp. 83–89 (1995).
Pairet M. et al., Proceedings of a conference, Oct. 10–11, 1995, "Improved Non–Steroid Anti–Inflammatory Drugs COX–2 Enzyme Inhibitors", Edited by John Vane et al., pp. 103–119.
Seibert K. et al., Advances in Prostaglandin, Thromboxane, and Leukotriene Research, vol. 23, p. 125–127 (1995).
Englehardt G., Br.J.Rheumatol. vol. 34, Abstr. Suppl. 1, p. 48 (1995).
Glaser K.B., Inflammopharmacology, vol. 3, pp. 335–345, (1995).
Gierse J.K. et al., Biochem.J., vol. 305, pp. 479–484 (1995).
Prasit P. et al., Med.Chem.Res., vol. 5, pp. 364–374 (1995).
Chan Chi–Chung et al., Journ.Pharmacology and Experimental Therapeutics, vol. 274, pp. 1531–1537 (1995).
Grossman C.J. et al., Inflammation Res., vol. 44, pp. 253–257 (1995).
Glaser K.B. et al., Inflammation Res., vol. 44, Suppl. 3, p. S276 (1995).
Grossman C.J. et al., Inflammation Res., vol. 44, Suppl. 3, p. S272 (1995).
Warner T.D. et al., Inflammation Res., vol. 44, Suppl. 3, p. S274 (1995).
Terlain B. et al., Presse Med., vol. 24, No. 10, pp. 491–496 (1995).
Gierse J.K. et al., Journ.Biological Chemistry, vol. 271, No. 26, pp. 15810–15814 (1996).
Englehardt G., Z. Rheumatol. vol. 55, Suppl. 1, p. 112 (1996).

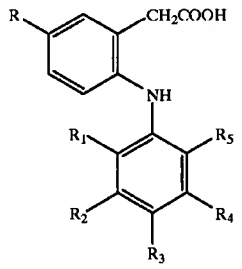
(List continued on next page.)

Primary Examiner—Robert Gerstl
(74) *Attorney, Agent, or Firm*—Norbert Gruenfeld

(57) **ABSTRACT**

Disclosed are the compounds of formula I

(I)



wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy; R_4 is hydrogen or fluoro; and R_5 is chloro, fluoro, trifluoromethyl or methyl; and pharmaceutically acceptable salts thereof, as selective COX-2 cyclooxygenase inhibitors; and pharmaceutically acceptable prodrug esters thereof.

36 Claims, No Drawings

US Express Mail EB907763642US

OTHER PUBLICATIONS

Distel M. et al., British Jour. of Rheumatology, vol. 35 (suppl. 1) pp. 68–77 (1996).
Churchill L. et al., Inflammopharmacology, vol. 4, pp. 125–135 (1996).
Steinhilber D., Pharm.Ztg., vol. 141(37), pp. 11–18 (1996).
Vane J.R. et al., Scan.J.Rheumatol. vol. 25 (Suppl. 102) pp. 9–21 (1996).
Matsushita M. et al., Inflamm.Res., vol. 46, pp. 461–466 (1997).
Englehardt G. et al., Biochemical Pharmacology, vol. 51, pp. 21–28 (1996).
Cromlish W.A. et al., Biochemical Pharmacology, vol. 52, pp. 1777–1785 (1996).
Brideau C. et al., Inflamm.Res., vol. 45, pp. 68–74 (1996).
Patrignani P. et al., Journal of Physiology and Pharmacology, vol. 48, 4, pp. 623–631 (1997).
Pairet M. et al., Proceedings of a conference on Mar. 20–21, 1997, "Selective COX-2 Inhibitors Pharmacology, Clinical Effects and Therapeutic Potential" Edited by John Vane et al., pp. 27–46.
Dammann H.G. et al., Clinical Pharmacology & Therapeutics, vol. 61, p. 162 (1997).
Pairet M. et al., Infamm. Res., vol. 47, Suppl. 2, pp. S93–S101 (1998).
Silvestre J. et al., Drugs of the Future, vol. 23(6), pp. 598–601 (1998).
Giuliano F. et al., Brit. J.Pharmacol., vol. 125, Suppl. 1, 35P (1998).
Simmons D.L. et al., Journal of Lipid Mediators, vol. 6, pp. 113–117 (1993).
Japanese Pharmacol. Ther., vol. 25, No. 8, pp. 2131–2136 (1997).
Japanese Journal of Inflammation, vol. 15, No. 5, pp. 409–411 (1995).
Cryer B. et al., Amer.J.Med., vol. 104, No. 5, pp. 413–421 (1998).

CERTAIN 5-ALKYL-2-ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application No. 60/069,837 filed Aug. 28, 1997 and of U.S. provisional application No. 60/057,803 filed Aug. 28, 1997.

BACKGROUND AND SUMMARY OF THE INVENTION

The invention relates to 5-alkyl-2-arylaminophenylacetic acids and derivatives thereof as defined herein which are particularly potent and selective cyclooxygenase-2(COX-2) inhibitors, methods for preparation thereof, pharmaceutical compositions comprising said compounds, methods of selectively inhibiting COX-2 activity and of treating conditions in mammals which are responsive to COX-2 inhibition using said compounds or pharmaceutical compositions comprising said compounds of the invention.

Various substituted 2-arylaminophenylacetic acids and derivatives thereof have been disclosed e.g. in J. Med. Chem. 33, 2358 (1990), U.S. Pat. Nos. 3,558,690, 3,652, 762, 4,173,577 and 4,548,952, and in PCT applications WO 94/104484, WO 97/09977, WO 96/00716 and DE 13,445, 011 as analgesic agents, non-steroidal antiinflammatory agents and cyclooxygenase inhibitors. As to 5-alkyl-2-arylaminophenylacetic acids, the only example known to be described in the literature is 5-methyl-2-(2,6-dimethylanilino)-phenylacetic acid and its sodium salt (U.S. Pat. No. 3,558,690) for which no biological data has been reported.

2-(2,6-Dichlorophenylamino) phenylacetoxyacetic acid (aceclofenac) and salts thereof have been disclosed e.g. in U.S. Pat. No. 4,548,952, and in PCT application WO 96/00716 as non-steroidal antiinflammatory and analgesic agents. The pharmacological properties of aceclofenac are apparently the result of in vivo conversion to diclofenac and/or derivatives thereof.

Non-steroidal antiinflammatory agents block prostaglandin synthesis by inhibition of the enzyme cyclooxygenase. Cyclooxygenase is now known to comprise a constitutive isoform (cyclooxygenase-1, COX-1) and an inducible isoform (cyclooxygenase-2, COX-2). COX-1 appears responsible for protective beneficial features of prostaglandins, e.g. for the gastrointestinal tract, kidney, etc., while the inducible isoform COX-2 appears responsible for pathological conditions associated with prostaglandins, such as inflammatory conditions. A limitation to the use of conventional nonsteroidal antiinflammatory drugs (NSAIDS), including aceclofenac and diclofenac sodium which is the sodium salt of 2,6-dichloroanilinophenylacetic acid, is gastrointestinal toxicity now attributed to the inhibition of the COX-1 isoform of cyclooxygenase. Selective inhibition of inducible COX-2 in vivo has been reported to be antiinflammatory and non-ulcerogenic (Proc. Natl. Acad. Sci. (U.S.A.) 1994; 91:3228–3232).

The present invention provides novel 5-alkyl substituted 2-arylaminophenylacetic acids and derivatives which surprisingly inhibit COX-2 without significantly inhibiting COX-1. The invention thus provides novel nonsteroidal antiinflammatory agents which are surprisingly free of undesirable side effects usually associated with the classical nonsteroidal antiinflammatory agents, such as gastrointestinal and renal side effects. The compounds of the present invention are thus particularly useful or may be metabolically converted to compounds which are particularly useful as COX-2 selective cyclooxygenase inhibitors. They are thus particularly useful for the treatment of cyclooxygenase-2 dependent disorders in mammals, including inflammation, pyresis, pain, osteoarthritis, rheumatoid arthritis, migraine headache, cancer such as digestive tract (e.g. colon) cancer and melanoma, neurodegenerative diseases (such as multiple sclerosis), Alzheimer's disease, osteoporosis, asthma, lupus and psoriasis while substantially eliminating undesirable gastrointestinal ulceration associated with conventional cyclooxygenase inhibitors. The compounds of the invention are also UV absorbers, in particular UV-B absorbers, and are useful for blocking or absorbing UV radiation, for instance for the treatment and prevention of sunburn, e.g. in suntan products.

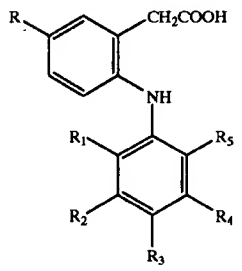
Ocular applications of the compounds of the invention include the treatment of ocular inflammation, of ocular pain including pain associated with ocular surgery such as PRK or cataract surgery, of ocular allergy, of photophobia of various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response (TIGR) protein and of dry eye disease.

The compounds of the present invention are useful for the treatment of neoplasia particularly neoplasia that produce prostaglandins or express cyclooxygenase, including both benign and cancerous tumors, growths and polyps, in particular epithelium cell-derived neoplasia. Compounds of the present invention are in particular useful for the treatment of liver, bladder, pancreatic, ovarian, prostate, cervical, lung and breast cancer and, especially gastrointestinal cancer, for example cancer of the colon, and skin cancer, for example squamous cell or basal cell cancers and melanoma, as indicated above.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy, e.g. in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or preclinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of premalignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g. squamous or basal cell carcinoma consequential to UV light exposure, e.g. resulting from chronic exposure to the sun.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compounds of formula I



(I)

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

pharmaceutically acceptable salts thereof; and

pharmaceutically acceptable prodrug esters thereof.

A particular embodiment of the invention relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof, and pharmaceutically acceptable prodrug esters thereof.

A preferred embodiment relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another preferred embodiment of the invention relates to compound of formula I wherein R is ethyl or methyl; R_1 is fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, ethoxy or hydroxy; R_4 is hydrogen or fluoro; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Further preferred are said compounds wherein R is methyl or ethyl; R_1 is fluoro; R_2–R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

A further embodiment of the invention relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen, ethoxy or hydroxy; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another preferred embodiment of the invention relates to the compounds of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; $R_4$is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof. Particular embodiments of the invention relate to compounds of formula I

(a) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof,

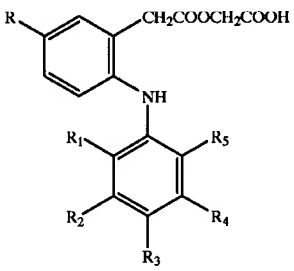
(b) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof;

(c) wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof; and

(d) wherein R is ethyl; R_1 is chloro; R_2 is hydrogen; R_3 is chloro; R_4 is hydrogen; and R_5 is methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

The general definitions used herein have the following meaning within the scope of the present invention.

Pharmaceutically acceptable prodrug esters are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I. Such esters are e.g. lower alkyl esters (such as the methyl or ethyl ester), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester), and the like. Preferred are the 5-alkyl substituted 2-arylaminophenylacetoxyacetic acids of formula Ia



(Ia)

wherein R and R_1–R_5 have meaning as defined hereinabove for compounds of formula I; and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts represent metal salts, such as alkaline metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed e.g. with ammonia and mono- or di-alkylamines, such as diethylammonium salts, and with amino acids, such as arginine and histidine salts.

A lower alkyl group contains up to 7 carbon atoms, preferably 1 to 4 carbon atoms and represents for example methyl, ethyl, propyl or butyl, and may be straight chain or branched.

The compounds of the invention are useful as selective cyclooxygenase-2 inhibitors or as prodrugs thereof. The selective cyclooxygenase-2 (COX-2) inhibitors and prodrugs thereof of the invention are particularly useful for the treatment of e.g. inflammation, pyresis, pain, osteoarthritis, rheumatoid arthritis and other conditions responsive to the inhibition of cyclooxygenase-2 and are typically substantially free of undesirable gastrointestinal side effects associated with conventional non-steroidal antiinflammatory agents.

The above-cited properties are demonstrable in vitro and in vivo tests using advantageously mammals, e.g. rats, mice, dogs, monkeys and isolated cells or enzyme preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. aqueous solutions, and in vivo advantageously orally, topically or parenterally, e.g. intravenously. The dosage in vitro may range from about 10^{-5} to 10^{-9} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 1 and 100 mg/kg.

Cyclooxygenase inhibition is determined in vitro using cellular assays for inhibition of both cyclooxygenase-1 and cyclooxygenase-2.

The cellular assays for testing cyclooxygenase inhibitors are based on the fact that the cyclooxygenase enzyme (prostaglandin H synthase) catalyzes the rate limiting step in prostaglandin synthesis from arachidonic acid. Two enzymes mediate the reaction: COX-1 is a constitutive form of the enzyme whereas COX-2 is induced in response to various growth factors and cytokines. Cell lines have been established which express one form of the enzyme: a human skin fibroblast line which can be induced with IL-1 to synthesize COX-2, and the kidney epithelial cell line 293 which has been stably transfected to constitutively express COX-1. Both isoforms metabolize arachidonic acid into the stable metabolite prostaglandin E_2. Arachidonic acid can be added exogenously to increase output to easily measurable levels. The levels of prostaglandin E_2 in the extracellular medium are assayed by radioimmunoassay as a measure of enzyme activity. The relative activities of each isoform are compared to assess compound selectivity.

In vitro cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition is determined in the cell-based assays in order to assess the in vitro activity and selectivity for COX-2 inhibition, using a prostaglandin E_2 radioimmunoassay. The cells utilized are primary human fibroblasts induced with interleukin-1 to produce COX-2, and the human kidney epithelial cell line 293 stably transfected to produce COX-1 constitutively. Cells are plated out into well plates in which the assay is performed. Fibroblasts are stimulated to synthesize COX-2 by treatment overnight with IL-1; the 293 cells require no induction. Both cell lines are pre-treated with compound dilutions for 15 minutes at 37° C., then 40 μM arachidonic acid is added as exogenous substrate for the production of PGE_2, which is measured in supernatant by radioimmunoassay. For IC_{50} determinations, compounds are tested at 5 concentrations in quadruplicate (highest concentration 30 μM); the mean inhibition of PGE_2 (compared to cells not treated with compound) for each concentration is calculated, a plot made of mean % inhibition vs. log compound concentration for all experiments, and the overall IC_{50} value calculated using a 4-parameter logistic fit.

IC_{50} values for compounds of formula I in the COX-2 inhibition assay are as low as about 0.005 μM whereas IC_{50} values in the COX-1 inhibition assay are greater than 30 μM.

Illustrative of the invention, the compounds of examples 1(d), 1(g) and 3(a) have an IC_{50} of about 0.13, 0.25, 0.007 μM, respectively, for COX-2 inhibition with no significant COX-1 inhibition at 30 μM.

The inhibition of prostaglandin-E_2 production produced by COX-2 can be determined in vivo in the lipopolysaccharide (LPS)-challenged subcutaneous air pouch model in the rat (see "Advances in Inflammation Research", Raven Press, 1986 and J. Med. Chem. 39, 1846 (1996)).

Female Lewis rats are anesthetized and then dorsal air pouches are prepared by subcutaneous injection of 10 ml of air through a sterile 0.45 micron syringe-adapted filter. Twenty-four hours after preparation, the air pouches are injected with LPS (8 μg/pouch) suspended in sterile phosphate buffered saline. Compounds for evaluation are suspended in fortified cornstarch and administered by gavage one hour prior to LPS challenge. The pouch contents are harvested three hours after LPS challenge and PGE_2 levels present in the pouch fluids are measured by enzyme immunoassay. ED_{50} values for inhibition of PGE_2 formation are calculated by least squares linear regression. Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a) and 6(a) have an ED_{50} in the range of about 0.2 mg/kg p.o. to about 0.6 mg/kg p.o.

The in vivo inhibition of thromboxane B_2 (TXB_2) produced by COX-1 can be measured ex vivo in the serum of rats after oral administration of compound.

Briefly, rats are fasted overnight, administered compound in fortified cornstarch vehicle by gavage, and sacrificed by carbon dioxide inhalation 30 minutes to eight hours later. Blood is collected by cardiac puncture into tubes without anti-coagulant, allowed to clot and serum is separated by centrifugation. Serum is stored frozen for later analysis of thromboxane B_2 by radioimmunoassay. Each experiment contains the following groups (5–6 rats per group): vehicle control and test compounds, either at different doses or different time points. Thromboxane B_2 data is expressed as a percentage of the levels measured in the vehicle control group.

Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a), and 6(a) cause less than a 50% inhibition of serum thromboxane B_2 production at an oral dose which is 50–150 times the ED_{50} value for in vivo COX-2 inhibition.

Antiinflammatory activity is determined using the carrageenan induced rat paw edema assay.

Sprague Dawley rats (200–225 g) are fasted overnight, then orally dosed with the compound suspended in a fortified cornstarch solution. After one hour, a 0.1 ml volume of 1% carrageenan in saline is injected into the subplantar region of the left hind paw which causes an inflammatory response. At 3 hours post carrageenan, the rats are euthanized and both hind paws are cut off at the paw hair line and weighed on an electronic balance. The amount of edema in the inflamed paw is determined by subtracting the weight of the non-inflamed paw (right) from the weight of the inflamed paw (left). The percent inhibition by the compound is determined for each animal as the percent paw weight gained as compared to the control average. ED_{30} values are determined for each dose-response using the curve fitting formula,

$$100/1+(\text{Drug Concentration}/ED_{30})^{slope}$$

Mean ED_{30} values are calculated as the average of ED_{30} values determined from independent dose response assays.

Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a) and 6(a) inhibit carrageenan-induced edema with an ED_{30} in the range of about 0.14 mg/kg p.o. to about 1.65 mg/kg p.o.

The gastric tolerability assay is used to assess gross ulceration in the rat, measured four hours after oral administration of the test compound. The test is carried out as follows: Rats are fasted overnight, administered compound in fortified cornstarch vehicle by gavage, and sacrificed by carbon dioxide inhalation four hours later. The stomachs are removed and gross gastric lesions counted and measured to give the total lesion length per rat. Each experiment contains the following groups (5–6 rats per group): vehicle control, test compounds, and diclofenac as a reference compound.

Data are calculated as the mean number of ulcers in a group, the mean length of ulcers (mm) in the group and as the ulcer index (UI).

UI=mean length of ulcers in a groupxulcer incidence

where ulcer incidence is the fraction of animals in the group with lesions (100% incidence is 1).

Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a) and 6(a) are essentially free of any gastric ulcerogenic effect at 100 mg/kg p.o.

Intestinal tolerability can be determined by measuring the effect on intestinal permeability. Lack of increase in permeability is indicative of intestinal tolerability.

The method used is a modification of a procedure by Davies, et al., Pharm. Res. 1994; 11:1652-1656 and is based on the fact that excretion of orally administered ^{51}Cr-EDTA, a marker of small intestinal permeability, is increased by NSAIDs. Groups of rats (≧12/group) are administered a single, oral dose of test compound or vehicle by gastric intubation. Immediately following compound dose, each rat is administered ^{51}Cr-EDTA (5 μCi/rat) by gastric intubation. The rats are placed in individual metabolic cages and given food and water ad libitum. Urine is collected over a 24 hour period. Twenty-four hours after administration of ^{51}Cr-EDTA the rats are sacrificed. To quantify compound effect on intestinal permeability, the excreted ^{51}Cr-EDTA measured in the urine of compound treated rats is compared to the excreted ^{51}Cr-EDTA measured in the urine of vehicle treated rats. Relative permeability is determined by calculating the activity present in each urine sample as a percent of the administered dose after correcting for background radiation.

Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a) and 6(a) demonstrate no effect or only a minimal effect on intestinal permeability at a dose of 30 mg/kg p.o.

The analgesic activity of the compounds of the invention is determined using the well-known Randall-Selitto assay.

The Randall-Selitto paw pressure assay measures antinociception (analgesic activity) in inflamed tissue by comparing the pressure threshold in the inflamed paw of the rat after oral administration of test drug with that in the inflamed paw of rats administered corn starch vehicle orally.

Groups of 10 male Wistar rats weighing 40–50 gms are fasted overnight prior to testing. Hyperalgesia is induced by the injection of 0.1 ml of a 20% suspension of Brewer's yeast with a 26 gauge needle into the subplantar region of the right hindpaw. The left paw is not injected and is used as the control paw for determination of hyperalgesia. Vehicle (Fortified corn starch suspension 3%) at 10 ml/kg, reference compound (diclofenac is run in every experiment at the same dose as test compounds) and test compounds at different doses suspended in vehicle at 1 ml/kg are administered orally 2 hours after the yeast injection. The threshold for paw withdrawal is quantified with a Basile Analgesymeter 1 hour after oral administration of test compounds. The nociceptive threshold is defined as the force in grams at which the rat withdraws its foot or vocalizes. Either vocalization or foot withdrawal is recorded as a response.

The data are analyzed by comparing the mean pain threshold of the corn starch vehicle-treated group for the inflamed and non-inflamed paws to that of individual drug-treated rats. Individual rats in the drug-treated groups and positive control (diclofenac) group are called reactors if the individual pain threshold in each paw exceeds the control group mean threshold by two standard deviations of that mean. The mean pain thresholds of the inflamed paw in the control group are compared to the individual pain thresholds of the inflamed paw in the test drug group. The non-inflamed control mean pressure threshold is compared to the non-inflamed individual pressure thresholds in the test groups. Results are expressed as number of reactors in each test group (n =10) for inflamed and non-inflamed paws. Percentages are calculated by dividing number of reactors by total number of rats used for a compound.

Illustrative of the invention, the compounds of examples 1(d), 1(g), 3(a) and 6(a) all increase the pain threshold in the inflamed paw at 10 mg/kg administered orally. These compounds selectively elevate the pain threshold in the inflamed paw with no threshold elevation in the non-inflamed paw indicating a peripheral mechanism.

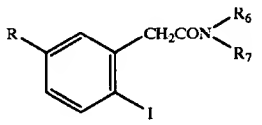
The antiarthritic effect of the compounds of the invention can be determined in the well-known chronic adjuvant arthritis test in the rat.

Ocular effects can be demonstrated in well-known ophthalmic assay methods. Similarly antitumor activity can be demonstrated in well-known antitumor animal tests.

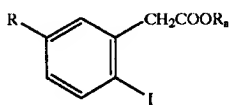
The compounds of formula I can be prepared e.g.

(a) by coupling a compound of formula II or IIa

(II)



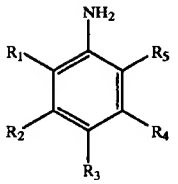
(IIa)



wherein R has meaning as defined above; R_a is lower alkyl, preferably isopropyl; and R_6 and R_7 represent lower alkyl; or R_6 and R_7 together with the nitrogen atom represent piperidino, pyrrolidino or morpholino;

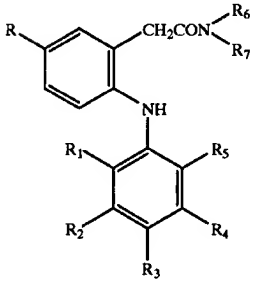
with a compound of formula III

(III)

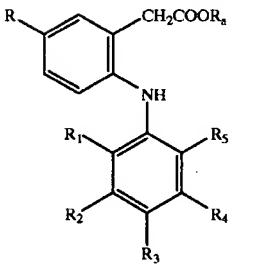


wherein R_1, R_2, R_3, R_4 and R_5 have meaning as defined above in the presence of copper and cuprous iodide to obtain a compound of formula IV or IVa

(IV)



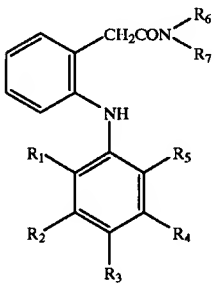
(IVa)



and hydrolyzing the resulting compound of formula IV or IVa to a compound of formula I; or

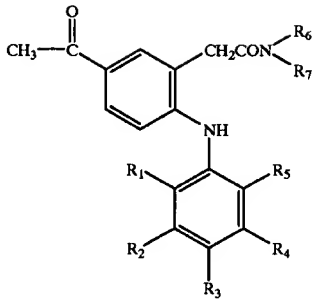
(b) for compounds in which R represents ethyl, by condensing a compound of formula V

(V)



wherein R_1–R_7 have meaning as defined herein, with a reactive functional derivative of acetic acid, such as acetyl chloride, in a Friedel-Crafts acylation to reaction to obtain a compound of the formula VI

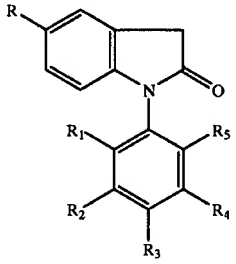
(VI)



wherein R_1–R_7 have meaning as defined herein which is in turn hydrogenolyzed and then hydrolyzed to obtain a compound of formula I wherein R represents ethyl; or

(c) by hydrolyzing a lactam of formula VII

(VII)



wherein R and R_1–R_5 have meaning as defined herein, with a strong base; and

in above processes, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting any resulting compound into another compound of the invention; and/or if desired converting a free carboxylic acid of the invention into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting a resulting free acid into a salt or a resulting salt into the free acid or into another salt.

In starting compounds and intermediates, which are converted to the compounds of the invention in a manner described herein, functional groups present such as amino, hydroxy and carboxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected hydroxy, amino and carboxyl groups are those that can be converted under mild conditions into free amino, hydroxy and carboxyl groups without other undesirable side reactions taking place. For example, hydroxy protecting groups are preferably benzyl or substituted benzyl groups, or acyl groups such as pivaloyl.

The preparation of compounds of formula IV according to process (a) is carried out under conditions of a modified Ullmann condensation for the preparation of diarylamines, e.g. in the presence of copper powder and copper (I) iodide and potassium carbonate, in an inert high boiling solvent such as nitrobenzene, toluene, xylene or N-methylpyrrolidone, at elevated temperature, e.g. in the range of 100°–200° C., preferably at reflux temperature,

according to general methodology described by F. Nohara, Chem. Abstr. 94, 15402x (1951) and Moser et al., J. Med. Chem. 33, 2358 (1990).

Intermediates of Formula IV wherein R_1, or R_5 is methyl or ethyl can be prepared from intermediates of formula IV, wherein R_1, or R_5 is bromo by reaction with tetramethyltin or tetraethyltin under conditions of a Heck reaction, that is in the presence of a palladium salt (such as $Pd(OAc)_2$ or $PdCl_2$), a triarylphosphine (such as tri (o-tolyl)phosphine) and a base (such as triethylamine, sodium acetate) in a polar solvent such as dimethylformamide.

Hydrolysis of the resulting ortho-anilinophenylacetamides of formula IV is carried out in aqueous alkali hydroxide, e.g. in 6N NaOH in the presence of an alcohol (e.g. ethanol, propanol, butanol) at elevated temperature, such as reflux temperature of the reaction mixture.

The hydrolysis of esters of formula IVa is carried out according to methods known in the art, e.g. under basic conditions as described above for the compounds of formula IV or alternatively under acidic conditions, e.g. using methanesulfonic acid.

The starting materials of formula 11 or Ha are generally known or can be prepared using methodology known in the art, e.g. as described by F. Nohara in Japanese patent application No. 78/96,434 (1978).

For example, 5-methyl or 5-ethylanthranilic acid is converted to the ortho-diazonium derivatives followed by treatment with an alkali metal iodide in acid (e.g. sulfonic acid) to obtain 5-alkyl-2-iodobenzoic acid. Reduction to the corresponding benzyl alcohol (e.g. with diborane), conversion of the alcohol first to the bromide and then to the nitrile, hydrolysis of the nitrile to the acetic acid and conversion to the N,N dialkylamide according to methodology known in the art yields a starting material of formula II.

Alternatively, the starting materials of formula II wherein R is ethyl can be prepared by Friedel-Crafts acetylation of oxindole with e.g. acetyl chloride in the presence of aluminum chloride, reduction of the resulting ketone by e.g. catalytic hydrogenolysis, followed by hydrolytic cleavage of the resulting 5-ethyloxindole to 5-ethyl-2-aminophenylacetic acid. Diazotization in the presence of e.g. potassium iodide yields 5-ethyl-2-iodo-phenylacetic acid which is converted to an amide of formula II. Esters of formula Ila are prepared from the corresponding acids according to esterification methods known in the art.

The anilines of formula III are either known in the art or are prepared according to methods well-known in the art or as illustrated herein.

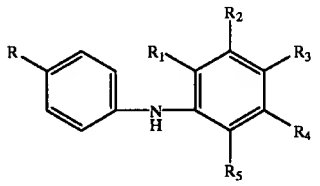
The preparation of 5-ethyl substituted compounds according to process (b) is carried out under conditions of Friedel-Crafts acylation e.g. in the presence of aluminum chloride in an inert solvent such as 1,2-dichloroethane, followed by hydrogenolysis, e.g. using palladium on charcoal catalyst, preferably in acetic acid as solvent, at room temperature and about 3 atmospheres pressure.

The starting materials of formula V are prepared generally as described under process (a) but starting with an amide of formula II in which R represents hydrogen, e.g. as described in J. Med. Chem. 33, 2358 (1990).

The preparation of the compounds of the invention according to process (c) can be carried out under conditions known in the art for the hydrolytic cleavage of lactams, preferably with a strong aqueous base, such as aqueous sodium hydroxide, optionally in the presence of an organic water miscible solvent such as methanol at elevated temperature in the range of about 50–100° C., as generally described in U.S. Pat. No. 3,558,690.

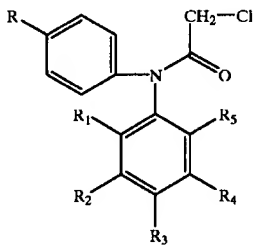
The oxindole starting materials are prepared by N-acylation of a diarylamine of the formula VII

(VIII)



wherein R and R_1–R_5 have meaning as defined above with a haloacetyl chloride, preferably chloroacetyl chloride, advantageously at elevated temperature, e.g. near 100° C., to obtain a compound of the formula IX

(IX)



wherein R and R_1–R_5 have meaning as defined hereinabove. Cyclization of a compound of formula IX is carried out under conditions of Friedel-Crafts alkylation in an inert solvent, such as dichlorobenzene, in the presence of Friedel-Crafts catalysts, e.g. aluminum chloride and ethylaluminum dichloride, at elevated temperature, e.g. at 120–175° C.

The diarylamines of formula VIII can be prepared by an Ullmann condensation and other methods known in the art, e.g. a Buchwald coupling reaction.

For example, the diarylamines of formula VIII wherein R_1, R_2, R_4 and R_5 are fluoro and R_3 is hydrogen can be prepared by reacting the corresponding aniline (4-ethyl- or 4-methyl-aniline) with pentafluorobenzene in the presence of a strong base such as lithium amide or n-butyllithium, as generally described in J. of Fluorine Chemistry 5, 323 (1975).

Esters of the carboxylic acids of formula I are prepared by condensation of the carboxylic acid, in the form of a salt or in the presence of a base, with a halide (bromide or chloride) corresponding to the esterifying alcohol (such as benzyl chloroacetate) according to methodology well known in the art, e.g. in a polar solvent such as dimethyl formamide, and if required further modifying the resulting product.

For example, if the esterification product is itself an ester, such can be converted to the carboxylic acid, e.g. by hydrogenolysis of a resulting benzyl ester. Also if the esterification product is itself a halide, such can for instance be converted to the nitrooxy derivative by reaction with e.g. silver nitrate.

For example, the compounds of formula Ia are preferably prepared by condensing a salt of a carboxylic acid of formula I above with a compound of formula

$$X—CH_2COOR_a$$

wherein X is a leaving group and R_a is a carboxy protecting group to obtain a compound of formula Ia in carboxy protected form, and subsequently removing the protecting group R_a.

The esterification can be carried under esterification conditions known in the art, e.g. in a polar solvent such as dimethylformamide, at a temperature range of room temperature to about 100° C., preferably at a range of 40–60° C.

The salt of the acid of formula I is preferably an alkali metal salt, e.g. the sodium salt which may be prepared in situ.

Leaving group X is preferably halo, e.g. chloro or bromo, or lower alkylsulfonyloxy, e.g. methanesulfonyloxy.

Carboxy protecting group R_a is preferably benzyl.

The resulting benzyl esters can be converted to the free acids of formula Ia preferably by hydrogenolysis with hydrogen in the presence of e.g. Pd/C catalyst in acetic acid at atmospheric pressure or under Parr hydrogenation at a temperature ranging from room temperature to about 50° C.

The invention includes any novel starting materials and processes for their manufacture.

Finally, compounds of the invention are either obtained in the free form, or as a salt thereof if salt forming groups are present.

The acidic compounds of the invention may be converted into metal salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained. Ammonium salts are obtained by reaction with the appropriate amine, e.g. diethylamine, and the like.

Compounds of the invention having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1–C_4)alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, for example glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or with organic sulfonic acids, such as (C_1–C_4)-alkylsulfonic acids (for example methanesulfonic acid) or arylsulfonic acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal, topical, and parenteral administration to mammals, including man, to inhibit COX-2-activity, and for the treatment of COX-2 dependent disorders, and comprise an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

More particularly, the pharmaceutical compositions comprise an effective cyclooxygenase-2 inhibiting amount of a selective cyclooxygenase-2 inhibiting compound of the invention which is substantially free of cyclooxygenase-1 inhibiting activity and of side effects attributed thereto.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, for example, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g. for the treatment of skin cancer, for example, for prophylactic use in sun creams, lotions, sprays and the like. In this regard it is noted that compounds of the

present invention are capable of absorbing UV rays in the range of 290–320 nm while allowing passage of tanning rays at higher wavelengths. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. Formulations suitable for topical application can be prepared e.g. as described in U.S. Pat. No. 4,784,808. Formulations for ocular administration can be prepared e.g. as described in U.S. Pat. Nos. 4,829,088 and 4,960,799.

The pharmaceutical formulations contain an effective COX-2 inhibiting amount of a compound of the invention as defined above, either alone or in combination with another therapeutic agent.

For example, suitable additional active agents for use in relation to the treatment of neoplasia include e.g. any of the anti-neoplastic agents or radioprotective agents recited in International patent application WO 98/16227.

In conjunction with another active ingredient, a compound of the invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg, of the active ingredient.

The present invention also relates to methods of using the compounds of the invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting COX-2 and for the treatment of COX-2 dependent conditions as described herein, e.g. inflammation, pain, rheumatoid arthritis, osteoarthritis, ocular inflammatory disorders, glaucoma and dry eye disease.

Particularly the present invention relates to a method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cycloxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of the invention.

Thus the present invention also relates to a method of treating cyclooxygenase-2 dependent disorders in mammals, which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of the invention.

More particularly the present invention relates to a method of treating cyclooxygenase-2 dependent disorders in mammals while substantially eliminating undesirable side effects associated with cyclooxygenase-1 inhibiting activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a selective cyclooxygenase-2 inhibiting compound of the invention which is substantially free of cyclooxygenase-1 inhibiting activity.

More specifically such relates to a method of e.g. treating rheumatoid arthritis, osteoarthritis, pain or inflammation in mammals without causing undesirable gastrointestinal ulceration, which method comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of the invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (≈20–133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art.

EXAMPLE 1

(a) N,N-dimethyl-5-methyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetamide (1.5 g, 4.3 mmol) is hydrolyzed with 6N NaOH (70 ml) as a two phase solution with n-BuOH (40 ml) at reflux temperature for 14 hours. After cooling to room temperature, the mixture is poured over ice (100 ml). Toluene (100 ml) is added and the mixture transferred to a separatory funnel. The aqueous phase is brought to a pH of 1 with 3 N HCl. The organic phase is separated and the aqueous phase re-extracted with toluene (100 ml). The combined organic solution is dried ($MgSO_4$) and concentrated under high vacuum (35–50 mbar), on a rotovap, taking care not to warm above 50°. Upon crystallization from Et_2O/hexane, 5-methyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetic acid is obtained as a tan solid, m.p. 137–141°.

The starting material, N,N-dimethyl-5-methyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetamide is prepared in the following manner:

5-Methyl-2-iodobenzoic acid (100 g, 0.38 mol) is dissolved in THF (350 ml) and cooled in an ice bath. Borane-THF complex (380 ml of 1M in THF, 0.38 mol) is added dropwise. After addition is complete, the reaction is warmed to room temperature and stirred for 14 hours. The mixture is transferred to a large erienmeyer flask, cooled in an ice bath, and carefully quenched with water (250 ml). Evaporation of the THF on a rotovap gives a white suspension which is treated with additional water (1 L) and then filtered and dried in a vacuum dessicator over P_2O_5 to give 2-iodo-5-methylbenzyl alcohol as a white solid, m.p. 82–85°.

The benzylic alcohol (99.8 g, 0.38 mol) is dissolved in 48% HBr (500 ml) and heated to reflux temperature for 4 hours. The resulting benzylic bromide is isolated as a yellow solid by pouring the cooled mixture into a large volume (1.5 L) of water followed by filtration. The benzylic bromide (caution: lachrymator) is dissolved in EtOH (400 ml) and stirred at room temperature. Sodium cyanide (56 g, 1.14 mol) is dissolved in a minimum amount (~100 ml) of water and then added to the ethanolic solution of the benzylic bromide. The reaction is heated to reflux temperature for 3 hours and then cooled to room temperature. Ethanol is removed on a rotovap and the residue washed with a large volume (1 L) of water. The resulting 2'-iodo-5'-methylphenylacetonitrile is isolated as a white solid, m.p. 77–790°, by filtration.

The nitrile (94.5 g, 0.37 mol) is dissolved in EtOH (350 ml) and treated with NaOH (29.4 g, 0.74 mol) which has been dissolved in water (200 ml). The reaction is heated to reflux temperature for 14 hours. After cooling to room

temperature, ethanol is removed on a rotovap and 6N HCl added until the pH=1. The solid 5-methyl-2-iodophenylacetic acid is filtered off and washed with water (2×500 ml). After drying over P_2O_5 in a vacuum dessicator, the solid 5-methyl-2-iodophenyl acetic acid (mp 112–114°, 83 g, 0.30 mol) is dissolved in CH_2Cl_2 (450 ml) that contains several drops of DMF. To the solution thionyl chloride (32 ml, 0.450 mol) is added and the reaction heated to reflux temperature overnight. After cooling to room temperature, the reaction mixture is diluted with additional CH_2Cl_2 (500 ml) and washed with water (2×250 ml), saturated $NaHCO_3$ (250 ml) and brine (250 ml). The solution is dried ($MgSO_4$) and concentrated on a rotovap to give 5-methyl-2-iodophenylacetyl chloride as a yellowish oil.

Dimethylamine (200 ml of 2 M solution in THF) is added dropwise to a solution of 5-methyl-2-iodophenylacetyl chloride in Et_2O (500 ml) which is cooled in an ice bath. After the addition is complete, EtOAc (350 ml) is added and the solution is washed with water (350 ml), brine (250 ml) and dried ($MgSO_4$). Evaporation on a rotovap and trituration with 1:1 Et_2O/hexanes gives N,N-dimethyl-5-methyl-2-iodophenylacetamide as a light tan solid, m.p. 47–49°.

N,N-Dimethyl-5-methyl-2-iodophenylacetamide (3.5 g, 11.5 mmol) and 2,4-dichloro-6-methylaniline (4.1 g, 23 mmol) are stirred in xylenes (100 ml) with copper powder (0.18 g, 2.9 mmol), copper(I) iodide (0.55 g, 2.9 mmol) and anhydrous potassium carbonate (1.6 g, 11.5 mmol). The reaction is heated to reflux temperature for 48 hours. While still slightly warm (40°) the brown suspension is filtered through a pad of Celite, which in turn is rinsed with toluene (75 ml). The filtrate is evaporated on a rotovap and flash chromatographed on silica gel (R_f 0.30 in 40% EtOAc/hexane) to give N,N-dimethyl-5-methyl-2-(2',4'-dichloro-6'-methylanilino) phenylacetamide as an off-white crystalline solid, m.p. 119–124°.

Similarly prepared are:

(b) 5-methyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetic acid, m.p. 153–156°;

(c) 5-methyl-2-(2',6'-dichloroanilino)phenylacetic acid, m.p.168–170°;

potassium salt, m.p. 318–320°; sodium salt, m.p. >300°;

(d) 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid, m.p. 158–159°;

(e) 5-methyl-2-(2',6'-dichloro-4'-methylanilino) phenylacetic acid, m.p. 179–182°;

(f) 5-methyl-2-(2'-chloro-6'-methylanilino)phenylacetic acid, m.p. 138–140°;

(g) 5-methyl-2-(2',4'-difluoro-6'-chloroanilino) phenylacetic acid, m.p. 157–159°;

(h) 5-methyl-2-(2'-fluoro-4',6'-dichloroanilino) phenylacetic acid, m.p. 178–180°;

(i) 5-methyl-2-(2'-chloro-4'-fluoro-6'-methylanilino) phenylacetic acid, m.p. 154–156°.

(j) 5-methyl-2-(2'-chloro-4'-hydroxy-6'-fluoroanilino) phenylacetic acid, m.p. 180–182°.

The starting material for compound of Example 1(j), 2-chloro-4-pivaloyloxy-6-fluoroaniline, is prepared in the following manner:

To a mixture of 7.0 g (0.045 mol) of 3-fluoro-4-nitrophenol and 6.7 g (0.067 mol) of triethylamine in 20 ml of methylene chloride cooled to 0° is added 6.5 g (0.054 mol) of pivaloyl chloride in a dropwise manner. The reaction is allowed to warm to room temperature and stirred overnight. The reaction is quenched with water and extracted with ethyl acetate. The organic layer is washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated brine, and then dried over magnesium sulfate. Filtration and removal of the solvents gives crude 2-fluoro-4-pivaloyloxy-nitrobenzene which is dissolved in 200 ml of absolute ethanol. To the solution is added 0.9 g of 5% palladium on carbon, and the mixture is then hydrogenated under 30 psi hydrogen for two hours. The catalyst is filtered and the solvent removed to give 2-fluoro-4-pivaloyloxyaniline.

A mixture of 7.3 g (0.035 mol) of 2-fluoro-4-pivaloyloxyaniline and 5.1 g (0.038 mol) of N-chlorosuccinimide in 50 ml of fluorobenzene is heated to reflux under a nitrogen atmosphere for two hours. After cooling to room temperature, the solvent is removed, water is added, and the mixture is extracted with ethyl acetate. The organic layer is washed with 1 N sodium hydroxide, and saturated brine, and dried over magnesium sulfate. Filtration and removal of the solvents gives a residue which is purified by silica gel chromatography (20% ethyl acetate/hexane) to give 2-chloro-4-pivaloyloxy-6-fluoroaniline. Conversion of 2-chloro-4-pivaloyloxy-6-fluoroaniline to 5-methyl-2-(2'-chloro-4'-hydroxy-6'-fluoroanilino)phenylacetic acid is carried out in a manner similar to that described in Example 1, the pivaloyl group being hydrolyzed in the last step along with the dimethylamide to give the final product.

EXAMPLE 2

Similarly prepared according to procedures described in Example 1 are:

(a) 5-ethyl-2-(2'-fluoro-6'-chloroanilino)phenylacetic acid, m.p. 147–148°;

The starting material, 5-ethyl-2-iodo-N,N-dimethylphenylacetamide is prepared as follows:

$AlCl_3$ (303 g, 2.27 mol) is placed in a 3-necked flask fitted with a thermometer and a dropping funnel. While stirring DMF (50 ml) is added dropwise and the temperature rises to about 60°. The mixture is cooled down to 45°, and oxindole (33 g, 0.25 mol) is added in 3 portions. After an additional 10 minutes, acetyl chloride (36 ml, 0.5 mol) is added. The mixture is stirred for an additional 30 minutes at room temperature. The mixture is poured onto ice (3000 g). This results in the formation of a solid which is filtered off, washed first with water and then with cold methanol (1000 ml), and then dried to give 5-acetyloxindole.

The 5-acetyloxindole (54 g, 308 mmol), acetic acid (400 ml) and palladium on carbon (10%, 5 g) are combined and treated with hydrogen for 14 hours at 55 psi. The catalyst is removed by filtering through a bed of Celite, the filtrate is concentrated under reduced pressure and the residue is treated with ether to give 5-ethyloxindole

5-Ethyloxindole (~54 g, ~335 mmol), ethanol (750 ml), water (150 ml) and potassium hydroxide (65 g, 1.62 mol) are combined and heated at reflux for 3 days. The mixture is allowed to cool and then filtered through a bed of Celite. The filtrate is concentrated under reduced pressure, water is added and the pH adjusted to 6.5. The precipitate is filtered off, washed with water and dried in an oven overnight to yield 5-ethyl-2-aminophenylacetic acid.

A mixture of water (405 ml) and concentrated HCl (48 ml) is stirred and cooled to 0°. 5-Ethyl-2-aminophenylacetic acid (53.7 g, 300 mmol) is slowly added while maintaining the temperature at 0–2°. After this addition a solution of sodium nitrite (22.2 g, 322 mmol) in 60 ml water is added dropwise over 30 minutes keeping the temperature at 0–2°. After a further 20 minutes a solution of potassium iodide (48 g, 290 mmol) in 18 ml conc HCl and 130 ml water is added dropwise while keeping the temperature below 10° C. The reaction mixture is allowed to warm to room temperature and then heated to reflux for 2 hours. The mixture is extracted with ethyl acetate and ether (1:1 mixture, 4×300 ml), the organic layer is then washed first with a 30% aqueous solution of sodium thiosulfite and then with a sodium hydroxide solution (0.1 M) before being acidified to pH 6 and extracted with ethyl acetate. This solution is washed with saturated brine, dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure. The residue is treated with hexane to yield 5-ethyl-2-iodophenylacetic acid.

5-Ethyl-2-iodophenylacetic acid is dissolved in methylene chloride (400 ml) and DMF (1 ml) is added. Thionyl chloride (21 ml, 300 mmol) is then added dropwise over 20 minutes. The mixture is heated to reflux and heating continued for 3.5 hours when the mixture is cooled and ice-water (400 ml) and methylene chloride (300 ml) are added. The layers are separated, the organic layer is washed with a sodium bicarbonate solution, saturated brine, dried (magnesium sulfate), and evaporated under reduced pressure to yield 5-ethyl-2-iodophenylacetyl chloride.

The acid chloride (46 g 150 mmol) is dissolved in ether (500 ml) and stirred at −35°. Dimethylamine (250 ml of 2M solution in THF, 500 mmol) is added dropwise at −35° and the mixture allowed to warm to room temperature and then stirred for 60 hours. Ethyl acetate and water are added and the layers separated. The organic layer is washed with saturated brine and the combined aqueous layers washed with ether. The combined organic layers are now dried (magnesium sulfate), and the solvent is removed under reduced pressure. Hexane is added to yield N,N-dimethyl 5-ethyl-2-iodophenylacetamide as a solid.

(b) 5-ethyl-2-(2'-chloro-6'-methylanilino)phenylacetic acid, m.p. 125–126°;

(c) 5-ethyl-2-(2',3',6'-trifluoroanilino)phenylacetic acid, m.p. 138–140°;

(d) 5-ethyl-2-(2',3',5',6'-tetrafluoro 4'-ethoxyanilino) phenylacetic acid, m.p. 131–132°;

(e) 5-ethyl-2-(2'-chloro-4',6'-difluoroanilino)phenylacetic acid, m.p. 160–162°;

(f) 5-ethyl-2-(2',4'-dichloro-6'-fluoroanilino)phenylacetic acid, m.p.169–171°.

EXAMPLE 3

(a) N,N-Dimethyl-5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetamide (26 g, 0.073 mol) and 6N NaOH (150 ml) are stirred as a two phase solution with n-BuOH (150 ml) at reflux temperature for 14 hours. After cooling to room temperature, the reaction is poured over ice (500 ml). Toluene (500 ml) is added and the mixture transferred to a separatory funnel. The aqueous phase is brought to a pH of 1 with 3 N HCl. The organic layer is separated and the aqueous phase re-extracted with toluene (250 ml). The combined organic layers are dried ($MgSO_4$) and concentrated under high vacuum (35–50 mbar) on a rotovap taking care not to warm above 500°. Small white needles are obtained by crystallization of the residue from hexane, m.p. 164–166°. Recrystallization from cyclohexane gives 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid a white solid, m.p. 165–169°.

The starting material N,N-dimethyl-5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetamide is prepared in the following manner

N,N-Dimethyl-2-iodophenylacetamide (60 g, 0.208 mol), 2',3',5',6'-tetrafluoroaniline (100 g, 0.606 mol), copper powder (6.6 g, 0.104 mol), copper(I) iodide (19.8 g, 0.104 mol) and anhydrous potassium carbonate (28.7 g, 0.208 mol) are stirred together in 1000 ml of xylenes. The reaction is heated to reflux temperature for 48 hours. While still slightly warm (40°) the brown suspension is filtered through a pad of Celite which in turn is rinsed with toluene (250 ml). The filtrate is evaporated on a rotovap and then flash chromatographed on silica-gel (Rf 0.25 in 30% EtOAc/hexane). Crystallization from pentane/Et_2O gives N,N-dimethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetamide, m.p. 109–110°.

Under an inert atmosphere, acetyl chloride (29.1 ml, 0.385 mol) is slowly added to a suspension of aluminum chloride (51.2 g, 0.385 mol) stirred in 1,2-dichloroethane (750 ml). After stirring at room temperature for 1 hour a yellow solution is obtained. The solution is cooled in an ice bath and N,N-dimethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetamide (40 g, 0.123 mol) is added.

The reaction is allowed to warm to room temperature and then warmed to 800° for 0.5 hours. The reaction is poured over ice and extracted with EtOAc (2×750 ml). The organic extract is washed with water (750 ml), saturated $NaHCO_3$ solution (500 ml) and brine (500 ml). Evaporation on a rotovap and trituration with Et_2O gives N,N-dimethyl-5-acetyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetamide as a white solid, m.p. 112–114°.

N,N-dimethyl-5-acetyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetamide (30 g, 0.802 mol) is dissolved in HOAc (150 ml) and hydrogenated (55 psi) with a 10% Pd/C (1.5 g) catalyst for 8 hours. The catalyst is removed by filtration through Celite and the filtrate poured into water (500 ml) and EtOAc (500 ml). The organic layer is washed with water (750 ml), neutralized with saturated Na_2CO_3 solution (500 ml) and washed with brine (500 ml). Evaporation on a rotovap followed by trituration with hexanes gives N,N-dimethyl-5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetamide, m.p. 105–106°.

Similarly prepared are:

(b) 5-ethyl-2-(2',4'-dichloro-6'-methylanilino) phenylacetic acid, m.p. 180–183°;

(c) 5-ethyl-2-(2',6'-dichloroanilino)phenylacetic acid, m.p. 133–136°.

EXAMPLE 4

(a) N-(2,3,5,6-tetrafluorophenyl)-5-ethyloxindole (72.67 g; 0.235 mol, is slurried in water containing a little methanol (10% v/v; 253 ml), and sodium hydroxide solution (50 wt %; 16.1 ml) is added. The mixture is stirred at 80–85° for 2–4

hours, then cooled to ambient temperature. The reaction solution is partially concentrated under reduced pressure (25–30 mm). After removal of 50 ml of the solvent, the mixture is diluted with water (150 ml) and t-butyl methyl ether (250 ml). The cooled mixture is acidified to pH 6.5–7.0 with aqueous HCl (12.1 N; 19.5 ml), keeping the temperature at 0–5°. The aqueous layer is discarded and the organic layer is washed with water (250 ml). The organic layer is concentrated under reduced pressure (20–100 mm) while exchanging the solvent to toluene. After the more volatile components have been removed, the batch volume is adjusted to 400–450 ml. This mixture is warmed to 700°, clarified, concentrated to one-half volume, and cooled to 0° After stirring at this temperature for 2 hours, the product is collected and is washed with toluene/heptane (10:90; 100 ml). The resulting solid is dried under reduced pressure at 50–60° for 4–8 hours to give 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetic acid of Example 3.

The starting material is prepared as follows: 4-Ethylaniline (242.36 g; 2.00 mol) is dissolved in dry tetrahydrofuran (900 ml). A solution of n-BuLi (2.5 M in hexanes, 800 ml; 2.00 mol) is added under N_2 with cooling maintaining the reaction temperature below 15°. After stirring for 1 hour at 10°, neat pentafluorobenzene (168.06 g; 1.00 mol) is added with cooling to the mixture, keeping the temperature at 10–200. The reaction is stirred at ambient temperature for 1.5 hours, then aqueous HCl (6 N; 500 ml) is added slowly with vigorous stirring and cooling, keeping the reaction temperature below 350°. The quenched reaction is stirred at ambient temperature for 0.5–18 hours. The aqueous layer is separated, and the organic phase is concentrated under reduced pressure (30–150 mm) to one-fourth volume. The concentrate is diluted with heptane (300 ml) and extracted with water (300 ml). The separated top organic layer is stirred over 230–400 mesh silica gel (50 g) and filtered. The filter cake is washed with heptane (4×50 ml). The combined filtrate and washings are concentrated under reduced pressure (20–30 mm) to give solid crude product. This material is recrystallized from hot heptane (200 ml) and collected at 0°. This solid is washed with cold heptane (100 ml) and dried under reduced pressure at 400 to give pure N-(2',3',5',6'-tetrafluorophenyl)4-ethylaniline.

The diphenylamine derivative (230.0 g; 0.854 mol; 1.0 eq) is treated with chloroacetyl chloride (192.96 g; 1.709 mol; 2.0 eq) at 100–115° for 2 hours (vigorous HCl evolution is controlled by rate of heating). The mixture is cooled to ambient temperature, then concentrated under reduced pressure (10–12 mm) to 80–90% of the original volume. 1,2-Dichlorobenzene (80 ml) is added and the diluted mixture is concentrated under reduced pressure (10–12 mm) until no more chloroacetyl chloride is found by GC analysis (30–40 ml distilled) to give crude N-(2',3',5',6'-tetrafluorophenyl)-N-chloroacetyl-4-ethylaniline in solution.

Anhydrous AlC_3 (170.84 g; 1.281 mol; 1.5 eq) was slurried with 1,2-dichlorobenzene (480 ml) under N_2 and cooled to 0°. The crude product solution from the previous step (theoretically containing 295.34 g; 0.854 mol; 1.0 eq) is added slowly with vigorous stirring, keeping the temperature below 60°. A solution of $EtAlCl_2$ (1.8M in toluene; 733 ml; 1.319 mol; 1.7 eq) is added, and the vigorously stirred reaction mixture is heated to ~160°, distilling toluene (135–160°) at ambient pressure. Upon cessation of the distillation (~690 ml), the reaction temperature is held at 155–165° for 3.5–5 hours. The mixture is cooled to ambient temperature, then poured onto crushed ice (2.5 kg) with vigorous stirring under N_2. The reaction vessel is rinsed with 1,2-dichlorobenzene (50 ml). The cold quenched product slurry is filtered and the filtercake is washed sequentially with 10% 1,2-dichlorobenzene/heptane (100 ml) and heptane (100 ml). The material is dried under reduced pressure at 80–90° for 12–16 hours to give N-(2',3',5',6'-tetrafluorophenyl)-5-ethyloxindole.

EXAMPLE 5

(a) N,N-Dimethyl 5-ethyl-2-(4'-chloro-2'-fluoro-6'-methylanilino)phenylacetamide is converted as in the previous examples to 5-ethyl-2-(4'-chloro-2'-fluoro-6'-methylanilino)phenylacetic acid, m.p. 153–156°.

The starting material is prepared as follows:

Ullmann condensation of N,N-dimethyl-5-ethyl-2-iodophenylacetamide with 2-bromo-4-chloro-6-fluoroaniline according to the procedure described in Example 1 yields N,N-dimethyl-5-ethyl-2-(2'-bromo-4'-chloro-6'-fluoroanilino)phenylacetamide.

N,N-Dimethyl-5-ethyl-2-(2'-bromo-4'-chloro-6'-fluoroanilino)phenylacetamide (2.5 g, 6.0 mmol) is combined with DMF (10 ml), triethylamine (10 ml), tri-o-tolylphosphine (0.5 g, 1.6 mmol), tetramethyltin (4 ml, 5.16g, 28.9 mmol) and palladium acetate (0.25 g, 1.1 mmol), and the mixture heated in a sealed tube for 3 days at 95°. The tube is allowed to cool and carefully opened. Water and ethyl acetate are added to the reaction and the mixture separated. The organic fraction is washed with a dilute NaCl solution (2×50 ml). The combined aqueous fractions are then washed with ethyl acetate and the combined organic fractions are then dried (magnesium sulfate). The material is absorbed onto a small amount of silica gel and purified by flash chromatography (on silica, ethyl acetate:hexanes, 1:4 to 1:1) to give N,N-dimethyl-5-ethyl-2-(4'-chloro-2'-fluoro-6'-methylanilino)phenylacetamide.

Similarly prepared are:

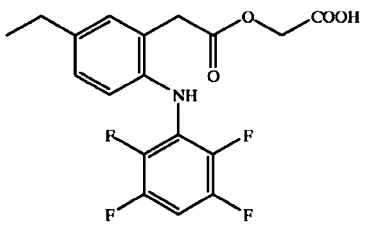
(b) 5-ethyl-2-(2',4'-difluoro-6'-methylanilino) phenylacetic acid, m.p. 143–145°;

(c) 5-ethyl-2-(2'-chloro-4'-fluoro-6'-methylanilino) phenylacetic acid, m.p. 151–154°;

EXAMPLE 6

(a) 5-Ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetic acid (1.0 g, 3.06 mmol) in THF (100 ml) is treated with 1 N sodium hydroxide (3.06 ml, 3.06 mmol) for 1 hour. The mixture is concentrated on a rotovap and then dried by evaporating first with THF (2×100 ml) and then with benzene (2×100 ml). The remaining off-white sodium salt of 5-ethyl-2',3',5',6'-tetrafluoroanilino)phenylacetic acid is dried under high vacuum overnight. Sodium 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetate (0.5 g, 1.43 mmol) and benzyl 2-bromoacetate (272 μl, 1.72 mmol) are stirred at 50° in dimethylformamide (50 ml) for 14 hours. The reaction mixture is cooled to room temperature and partitioned between EtOAc (200 ml) and water (200 ml). The

organic layer is washed again with water (2x200 ml), brine (100 ml), dried ($MgSO_4$) and concentrated on a rotovap. The crude benzyl ester is flash chromatographed on silica (10–15% EtOAc/hexane) to provide the benzyloxycarbonylmethyl ester of 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid as a colorless oil. The oil is dissolved in HOAc (20 ml) and hydrogenated (55 psi) with a 10% Pd/C (0.1 g) catalyst for 1 hour. The catalyst is removed by filtration through Celite and the filtrate poured into water (200 ml) and EtOAc (200 ml). The organic layer is washed with water (250 ml) and brine (100 ml). Evaporation on a rotovap and trituration with Et_2O/hexanes gives the ester, carboxymethyl 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetate, m.p. 151–153°, of the formula



Similarly prepared are:

(b) carboxymethyl 5-ethyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetate, m.p. 123–125°;

(c) carboxymethyl 5-ethyl-2-(2',6'-dichloroanilino) phenylacetate, m.p.124–126°;

(d) carboxymethyl 5-ethyl-2-(2',4'-difluoro-6'-chloroanilino)phenylacetate, m.p.142–144°;

(e) carboxymethyl 5-ethyl-2-(2',4'-dichloro-6'-fluoroanilino)phenylacetate, m.p. 132–134°;

(f) carboxymethyl 5-ethyl-2-(2'-chloro-6'-fluoroanilino) phenylacetate, m.p. 106–108°;

(g) carboxymethyl 5-methyl-2-(2'-fluoro-4',6'-dichloroanilino)phenylacetate, m.p. 148–150°;

(h) carboxymethyl 5-methyl-2-(2',6'-dichloroanilino) phenylacetate, m. p.125–126°;

(i) carboxymethyl 5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetate, m.p. 96–98°.

(j) carboxymethyl 5-methyl-2-(2',4'-difuoro-6'-chloroanilino)phenylacetate.

EXAMPLE 7

5-Ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetic acid (1.0 g, 3.06 mmol) in THF (100 ml) is treated with 1 N sodium hydroxide (3.06 ml, 3.06 mmol) for 1 hour. The mixture is concentrated on a rotovap and the residue is then treated and evaporated to dryness first with THF (2x100 ml) and then with benzene (2x100 ml). The remaining off-white sodium salt of 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid is dried under high vacuum overnight.

The sodium 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetate (2.0 g, 6.2 mmol) is dissolved in DMF (70 ml) and treated with 1-bromo- 4-chlorobutane (1.2 g, 6.9 mmol) at room temperature overnight. The reaction mixture is concentrated under high vacuum (35–50 mbar) on a rotovap. The resulting oil is partitioned between water (200 ml) and Et_2O (200 ml). The organic layer is washed with brine (100 ml), dried ($MgSO_4$) and concentrated on a rotovap to give the chlorobutyl ester as a light-brown oil. The chlorobutyl ester is dissolved in CH_3CN (100 ml) and treated with silver nitrate (8.7 g, 50 mmol) at reflux temperature for 18 hours. The reaction is cooled to room temperature and the solvent removed on a rotovap. The residue is partitioned between CH_2Cl_2 (200 ml) and water (200 ml). The organic layer is dried ($MgSO_4$), concentrated and flash-chromatographed (5% EtOAc/hexane) to give nitrooxybutyl 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetate as a clear oil.

EXAMPLE 8

Sodium 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetate (7.3 g, 20.9 mmol) is dissolved DMF (100 ml) and treated with benzyl 2-methyl-2-bromopropionate (6.2 g, 24.2 mmol) at 500 for 96 hours. The reaction mixture is cooled to room temperature, and concentrated under high vacuum (35–50 mbar) on a rotovap. The resulting oil is partitioned between water (200 ml) and Et_2O (200 ml). The organic layer is washed with brine (100 ml), dried ($MgSO_4$) and concentrated on a rotovap to give a light-brown oil. Flash chromatography (0–10% EtOAc/hexane) on silica-gel gives the ester as a light-red oil. The ester (1.5 g, 3.0 mmol) is dissolved in EtOAc (150 ml) and hydrogenated (55 psi) with a 10% Pd/C (0.3 g) catalyst for 1 hour. The catalyst is removed by filtration through Celite (500 ml). Evaporation on a rotovap followed by trituration with hexanes gives 1-carboxy-1-methylethyl 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetate as a crystalline white solid, m.p. 104–108°.

EXAMPLE 9

(a) Isopropyl 5-methyl-2-(2'-fluoro-6'-trifluoromethylanilino)phenylacetate (2.9 g, 8.4 mmol) is dissolved in methanesulfonic acid (25 ml) and stirred at room temperature for 8 hours. The reaction mixture is slowly added to 200 ml of ice in a beaker. After the ice has melted, the solution is stirred to produce a white solid which is isolated by filtration. The solid is flash chromatographed on silica-gel using 35% EtOAc as an eluant to give 5-methyl-2-(2'-fluoro-6'-trifluoromethylanilino) phenylacetic acid as a white solid, m.p. 155–156°.

The starting material is prepared as follows:

2-Iodo-5-methylphenylacetic acid (20.0 g, 72 mmol) and a catalytic amount of 98% sulfuric acid (0.2 ml) are dissolved in isopropyl alcohol (200 ml) and heated to reflux temperature for 48 hours. The solvent is removed on a rotovap and the residual oil partitioned between EtOAc (500 ml) and saturated $NaHCO_3$ solution (500 ml). The organic layer is separated, dried ($MgSO_4$) and concentrated on a rotovap. The residual oil is distilled using a kugelrohr apparatus to give a clear, colorless oil which solidifies on standing at room temperature to give isopropyl 2-iodo-5-methylphenylacetate, m.p. 48–50°.

Isopropyl 2-iodo-5-methylphenylacetate (10.0 g, 31 mmol), 2-amino-3-fluorobenzotrifluoride (20.0 g, 111 mmol), copper powder (1.1 g, 16 mmol), copper (I) iodide (3.1 g, 16 mmol) and K_2CO_3 (4.3 g, 31 mmol) are stirred together in xylenes (200 ml). The reaction mixture is heated to reflux temperature for 48 hours. While still slightly warm (400) the brown suspension is

filtered through a pad of Celite, which in turn is rinsed with toluene (100 ml). The filtrate is evaporated on a rotovap and then flash chromatographed on silica-gel using 34% EtOAc in hexanes as the eluant. The product, isopropyl 5-methyl-2-(2'-fluoro-6'-trifluoromethylanilino)phenyl acetate, is isolated as a pale yellow oil.

(b) Similarily prepared is 5-methyl-2-(2',4'-dichloro-6'-trifluoromethylanilino)phenylacetic acid, m.p. 157–158°.

EXAMPLE 10

(a) To a degassed solution of 1500 ml of absolute ethanol and 510 ml of 2N NaOH (1.02 mol) is added 150 g (0.51 mol) of N-(2'-chloro-4',6'-difluorophenyl)-5-methyloxindole. The resultant mixture is degassed and heated to 60–65° for 2 hours. Most of the ethanol is removed under reduced pressure and then 4500 ml of water is added to the residue which is then washed three times with 1500 ml of toluene. The aqueous layer is cooled to 0° and adjusted to pH 6 using 1.2 N HCl. The solid is filtered off and washed with 100 ml of water and dried. Recrystallization from ethyl acetate and heptane gives 5-methy-2-(2',4'-difluoro-6-chloroanilino)phenylacetic acid of Example 1(g).

The starting material is prepared in the following manner: 2-Bromo-4,6-difluoroaniline (26.00 g; 0.13 mol) is added to 78 ml (0.71 mol) of acetic anhydride and stirred at room temperature for 5 hours. The reaction is quenched by the addition of 104 ml of water over a 10 minute period, causing the temperature to rise to 43°. The reaction is allowed to cool to room temperature and then cooled to 5° in ice water. The solids are collected by suction filtration, washed with 104 ml of water, and dried to give 2-bromo-4,6-difluoroacetanilide, m.p. 156°.

Cuprous chloride (11.9 g, 0.12 mol) and cupric chloride (16.14 g, 0.12 mol) are dissolved in 100 ml of DMF. 2-Bromo-4,6-difluoroacetanilide (20 g, 0.08 mol) is added and the solution is heated to 130° C. for 20 hours. The reaction is cooled to room temperature and then added dropwise over 30 minutes to 400 ml of 3N HCl. The solid is filtered off, washed with 200 ml of water, and dried to give 2-chloro-4,6-difluoroacetanilide, m.p. 144–150°.

To a slurry of 110.36 g (0.54 mol) of 2-chloro-4,6-difluoroacetanilide in 735 ml of absolute ethanol is added 100.36 ml (1.32 mol) of concentrated HCl. The mixture is heated to reflux for 20 hours and then cooled to room temperature. The mixture is concentrated under reduced pressure to give a residue which is dissolved in 1105 ml of water, and 1N NaOH is added to adjust the pH to 12. The basic mixture is extracted twice with ethyl acetate and the combined organic layers are washed with 735 ml of water. The solvents are evaporated under reduced pressure to give 2-chloro4,6-difluoroaniline as an oil.

A mixture of 4-iodotoluene (210 g, 0.96 mol), 2-chloro-4,6-difluoroaniline (204 g, 1.25 mol), copper powder (36 g, 0.57 mol), cuprous iodide (130 g, 0.68 mol), and potassium carbonate (118 g, 0.86 mol) in 500 ml of xylene is stirred vigorously and heated to reflux in a flask fitted with a Dean-Stark trap for 26 hours. After cooling to room temperature, the solids are filtered off, and the filter cake is washed with 100 ml of xylene. The solvents are evaporated under reduced pressure to give an oil which is dissolved in a mixture of 50 g of silica gel in 750 ml of heptane. The solids are filtered off and the solvents are evaporated under reduced pressure to give N-(2'-chloro-4',6'-difluorophenyl)-4-methylaniline as an oil.

A mixture of 230 g (0.9 mol) N-(2'-chloro-4',6'-difluorophenyl)-4-methylaniline and 325 ml (4.06 mol) of chloroacetyl chloride is heated under a nitrogen atmosphere for one hour at 50°. The solvent is evaporated under reduced pressure to give an oil to which 200 ml of chlorobenzene is added. The solvent is evaporated under reduced pressure to completely remove the chloroacetyl chloride, giving N-(2'-chloro4',6'-difluorophenyl)-N-chloroacetyl-4-methylaniline as an oil.

To a mixture of 100 g (0.3 mol) of N-(2'-chloro-4',6'-difluorophenyl)-N-chloroacetyl-4-methylaniline and 103 g (0.78 mol) of aluminum chloride is added 400 ml of 1,2-dichlorobenzene. The reaction is heated to 140° for 2 hours. The reaction is cooled to room temperature and added to a mixture of 100 ml of concentrated HCl and 700 ml water (cooled to 0–5° in a dry ice/acetone bath). The mixture is extracted twice with 400 ml of methylene chloride. The combined organic layers are washed with 600 ml of 3N HCl. The organic layer is stirred with 66 g of magnesium sulfate and 33 g of charcoal (DARCO G-60). The solids are filtered off and the solvents are evaporated under reduced pressure to give a tan solid which is recrystallized from ethanol to give N-(2'-chloro-4',6'-difluorophenyl)-5-methyloxindole, mp 137–14°.

b) Similarly prepared is 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid of example 1 (d).

The preparation of the starting material, N-(2-chloro-6-fluoro)aniline from 2-chloro-6-fluorobenzamide is described in Rec. Trav. Chim. Pays-Bas, 97, 51–56 (1978).

EXAMPLE 11

A solution of 1300 ml of ethanol, 130 ml of water and 43.5 g of sodium hydroxide is degassed. To the solution is added 100.0 g of N-(2'-chloro-6'-fluorophenyl)-5-methyloxindole and the mixture is heated to 70° for 2 hours. The reaction is cooled to 50° and 90.7 ml of 37% HCl in 453.3 ml of water is added slowly. The suspension is cooled slowly to room temperature and filtered. The filter cake is washed three times with 80 ml of 1:1 ethanol and water and dried to give 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid, m.p. 152–154°.

The starting material, N-(2'-chloro-6'-fluorophenyl)-5-methyloxindole, is prepared in the following manner:

A solution of 261.1 g (2.0 mol) of 1-chloro-3-fluorobenzene in 2000 ml of dry tetrahydrofuran under nitrogen is cooled to −78°. To the solution is added 960 ml (2.4 mol) of 2.5 M n-butyllithium in hexanes over a period of 40 minutes. After stirring for 2.5 hours, a slurry of 155 ml of bromine cooled to −78° is added over 30 minutes and the mixture is stirred for 40 minutes before warming to −10°. The reaction is quenched with an aqueous solution of 151.3 g (1.2 mol) of sodium sulfite and 16.0 g (0.4 mol) of sodium hydroxide in 500 ml of water. The organic layer is separated, the solvents are removed at ambient pressure, and the product is distilled at 92–96° (20 mm Hg) to obtain 2-bromo-3-fluoro-chlorobenzene as a colorless oil.

A mixture of 146.1 g (1.36 mol) of p-toluidine, 12.6 g (0.02 mol) of (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 261.9 g (2.73 mol) of sodium t-butoxide, 314.1 g (1.50 mol) of 2-bromo-3-fluoro-chlorobenzene and 6.3 g (0.0069 mol) of tris(dibenzylideneacetone)dipalladium(0) in 3000 ml of toluene is heated to 110° over 30 minutes and stirred an additional 4 hours at this temperature. The mixture is cooled to room temperature and a solution of 680 ml 37% hydrochloric acid and 680 ml of water is added over 15 minutes. The mixture is stirred for 20 minutes and filtered through a pad of Celite. The layers are separated and the organic phase is washed twice with 680 ml of water and once with a solution of 225 g of sodium chloride in 680 ml of water. The solvents are evaporated under reduced pressure to give N-(2'-chloro-6'-fluorophenyl)-4-methylaniline as an oil, b.p. 129–131°/0.5 mm Hg.

A mixture of 25 g (0.11 mol) N-(2'-chloro-6'-fluorophenyl)-4-methylaniline and 40 ml (0.5 mol) of chloroacetylchloride is heated under a nitrogen atmosphere for 15 minutes at 60°. The solvent is evaporated under reduced pressure to give an oil which is dissolved in 25 ml of ethyl acetate. Pentane (250 ml) is added dropwise over 15 minutes to precipitate the product. The mixture is cooled to −15° C. and the solid is filtered and washed with pentane to give N-(2'-chloro-6'-fluorophenyl)-N-chloroacetyl4-methylaniline, m.p. 80–83°.

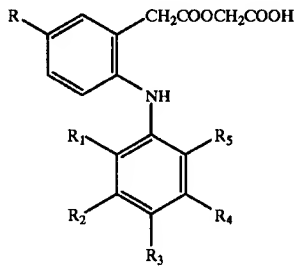
A mixture of 100 g (0.32 mol) of N-(2'-chloro-6'-fluorophenyl)-N-chloroacetyl-4-methylaniline and 110 g (0.82 mol) of aluminum chloride in 400 ml of 1,2-dichlorobenzene is stirred vigorously and heated to 140° for 7.5 hours. The reaction is cooled to room temperature and added to a mixture of 100 ml of 12N HCl and 700 ml of water (cooled to 0–5° in a dry ice/acetone bath). The mixture is extracted twice with 400 ml of methylene chloride and the combined organic layers are washed with 600 ml of 3N HCl. The organic layer is stirred with 66 g of magnesium sulfate and 33 g of charcoal (DARCO G-60). The solids are filtered through a pad of Celite and the solvents are evaporated under reduced pressure to give a tan solid which is recrystallized from ethanol to give N-(2'-chloro-6'-fluorophenyl)-5-methyloxindole, m.p. 137–140°.

Alternatively, a mixture of 169.8 g of crude N-(2'-chloro-6'-fluorophenyl)-4-methylaniline, 172 ml (2.15 mol) of chloroacetyl chloride in 580 ml of toluene is heated under a nitrogen atmosphere for 2 hours at 70°. The reaction is cooled to room temperature, 450 ml of decane is added, and the volatiles are distilled off under 200 mbar pressure at 62–72°. To the mixture is added 150 ml of toluene and 385 g of aluminum chloride (2.87 mol) slowly at 20–40°. The mixture is heated at 120° for 5 hours, cooled to 20°, and added over 30 minutes to 800 ml of ethyl acetate. The mixture is quenched by addition to a pre-cooled solution of 67 ml of 37% hydrochloric acid in 800 ml of water at 20±10°, and the resultant mixture is filtered through a pad of Celite. The organic layer is separated and the volatiles are distilled off. To the residue is added 100 ml of heptane and the mixture is cooled to 0° over a 30 minute period and stirred for one hour. The mixture is filtered and the filter cake is washed three times with 45 ml of heptane. To the crude product is added 90 g of charcoal (DARCO G-60) and 4500 ml of methanol. The mixture is heated to reflux for two hours, cooled to room temperature, and filtered through a pad of Celite. After distilling off 4390 ml of methanol, the mixture is cooled to 15°. The product is collected by filtration, washed three times with 30 ml of methanol, and dried to give N-(2'-chloro-6'-fluorophenyl)-5-methyloxindole.

What is claimed is:

1. A compound of formula

(12)



wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim **1** wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim **1** wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim **1** wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen, ethoxy or hydroxy; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim **1** wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim **1** which is carboxymethyl 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetate wherein in formula I R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **1** which is carboxymethyl 5-methyl-2-(2',4'-difluoro-6'-chloroanilino) phenylacetate wherein in formula I R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 which is carboxymethyl 5-ethyl-2-(2',3',5',6',-tetrafluoroanilino)phenylacetate wherein in formula I R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 which is carboxymethyl 5-ethyl-2-(2'4'-dichloro-6'-methylanilino) phenylacetate wherein in formula I R is ethyl; R_1 is chloro; R_2 is hydrogen; R_3 is chloro; R_4 is hydrogen; and R_5 is methyl; or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 1 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

11. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 6 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

12. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 17 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

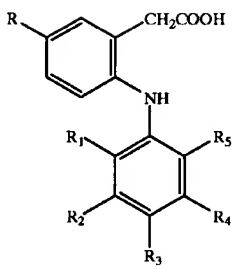
13. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 8 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

14. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 9 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

15. A method of treating cyclooxygenase dependent disorders in mammals without causing undesirable gastrointestinal side effects which comprises administering to a mammal in need thereof an effective amount of a compound according to claim 1 which is substantially free of gastrointestinal ulceration.

16. A method of treating rheumatoid arthritis, osteoarthritis, pain or inflammation in mammals without causing undesirable gastrointestinal side effects which comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of claim 1 which is substantially free of gastrointestinal ulceration.

17. A method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cycloxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I



(I)

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy or ethoxy;

R_4 is hydrogen or fluoro;

R_5 is chloro, fluoro or trifluoromethyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutically acceptable prodrug ester thereof.

18. A method according to claim 17 wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro or methyl; R_4, is hydrogen; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

19. A method according to claim 17 wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

20. A method according to claim 17 wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen or ethoxy; R4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

21. A method according to claim 17 wherein the compound is a compound of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

22. A method according to claim 17 wherein the compound is a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2–R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

23. A method according to claim 17 wherein the compound is 5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen; R4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

24. A method according to claim 17 wherein the compound is 5-methyl-2-(2',4'-difluoro-6'-chloroanilino) phenylacetic acid of formula I wherein R is methyl; R_1 is

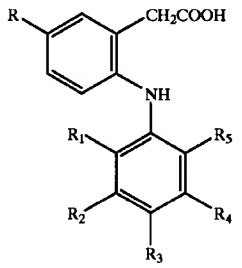
fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

25. A method according to claim **17** wherein the compound is 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid of formula I wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof.

26. A method according to claim **23** wherein the compound is 5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid.

27. A selective cyclooxygenase-2 inhibiting pharmaceutical composition substantially free of cyclooxygenase-1 inhibiting activity comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I

(I)



wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy or ethoxy;

R_4 is hydrogen or fluoro;

R_5 is chloro, fluoro or trifluoromethyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutically acceptable prodrug ester thereof;

in combination with one or more pharmaceutically acceptable carriers.

28. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro; chloro or methyl; R_4 is hydrogen; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.

29. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.

30. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen or ethoxy; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.

31. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; $R_3$is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.

32. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount which amount is substantially free of cyclooxygenase-1 inhibiting activity, of a compound of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2–R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof; in combination with one or more pharmaceutically acceptable carriers.

33. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclodxygenase-2 inhibiting amount which amount is substantially free of cyclooxygenase-1 inhibiting activity, of 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; $R_3$is hydrogen; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; in combination with one or more pharmaceutically acceptable carriers.

34. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of 5-methyl-2-(2',4'-difluoro-6'-chloroanilino) phenylacetic acid of formula I wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; in combination with one or more pharmaceutically acceptable carriers.

35. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **27** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cyclooxygenase-1 inhibiting activity, of 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino) phenylacetic acid formula I wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof; in combination with one or more pharmaceutically acceptable carriers.

36. A selective cyclooxygenase-2 inhibiting pharmaceutical composition according to claim **33** comprising an effective cyclooxygenase-2 inhibiting amount, which amount is substantially free of cycloxxygenase-1 inhibiting activity, of 5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid; in combination with one or more pharmaceutically acceptable carriers.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

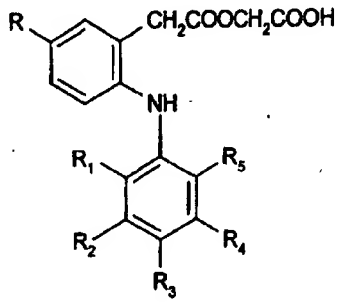
CERTIFICATE OF CORRECTION

PATENT NO. : 6,291,523 B1
DATED : September 18, 2001
INVENTOR(S) : Fujimoto et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75] should read:
-- [75] Inventors: **Roger A. Fujimoto,** Morristown; **Leslie W. McQuire,** Warren; **Benjamin B. Mugrage,** Basking Ridge; **John H. van Duzer,** Asbury, all of NJ (US) --

Column 28,
Lines 10-25 should read:
-- 1. A compound of formula



(Ia)

--

Column 29,
Line 26 should read:
-- antiinflammatory amount of a compound of claim 7 which --

Signed and Sealed this

Twenty-eighth Day of May, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Exhibit E- Maint. Fee Statement

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United States Patent and Trademark Office

Patent Bibliographic Data					04/21/2011 04:51 PM
Patent Number:	6291523		**Application Number:**	09139254	
Issue Date:	09/18/2001		**Filing Date:**	08/25/1998	
Title:	CERTAIN 5-ALKYL-2-ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES				
Status:	12th year fee window opens: 09/18/2012			**Entity:**	Large
Window Opens:	09/18/2012	**Surcharge Date:**	03/19/2013	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1553	MAINTENANCE FEE DUE AT 11.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	02/18/2009 02/28/2005	Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	NOVARTIS CORPORATE INTELLECTUAL PROPERTY ONE HEALTH PLAZA 101/2 EAST HANOVER, NJ 079361080				

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Patent Number: 6291523

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EAST HANOVER NJ 07936-1080

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,291,523	$2,480.00	$0.00	02/18/09	09/139,254	09/18/01	08/25/98	08	NO	NOVARTIS AG, BASEL, SWITZ

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Exhibit F - FOI Summary

I. GENERAL INFORMATION:

A. File Number:	NADA 141-320
B. Sponsor:	Novartis Animal Health US, Inc. 3200 Northline Ave, Suite 300 Greensboro, North Carolina 27408 Drug Labeler Code: 058198
C. Proprietary Name(s):	ONSIOR tablets
D. Established Name(s):	Robenacoxib
E. Pharmacological Category:	Non-steroidal anti-inflammatory drug (NSAID)
F. Dosage Form(s):	Non-scored tablet
G. Amount of Active Ingredient(s):	Each tablet contains 6 mg robenacoxib
H. How Supplied:	ONSIOR tablets are available as 6 mg round, flavored tablets in blisters. Each individual blister card contains 3 tablets. Ten blister cards are supplied in a carton. Each blister card should be dispensed in an ONSIOR dispensing envelope containing the product insert/information for owner sheet, supplied with the product.
I. How Dispensed:	Rx

US Express Mail EB 907763642 US

J. Dosage(s):

The dose of ONSIOR (robenacoxib) tablets is 0.45 mg/lb (1 mg/kg) orally once daily, for a maximum of three days.
Preoperatively: Administer dose approximately 30 minutes prior to surgery.
Postoperatively: Tablets may be given with or without food. See dosing chart for dosage directions.
Dosing Directions: to be used in cats ≥ 6 months of age and ≥ 5.5 lbs. Tablets are not scored and should not be broken.

Body weight	6 mg ONSIOR (robenacoxib) Tablet
5.5 to 13.2 lbs (2.5 to 6 kg)	1 whole tablet once daily
13.3 to 26.4 lbs (6.1 to 12 kg)	2 whole tablets once daily

K. Route(s) of Administration:

Oral

L. Species/Class(es):

Cats

M. Indication(s):

ONSIOR tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats ≥ 5.5 lbs (2.5 kg) and ≥ 6 months of age; for up to a maximum of 3 days.

II. EFFECTIVENESS:

A. Dosage Characterization:

A dose of 0.45 mg/lb (1 mg/kg) administered orally once daily for up to three treatments was selected based on the results of the following experimental studies.

A kaolin-induced acute pain and inflammation model study was performed in 10 European short-haired cats of both sexes in a single dose pharmacokinetic/pharmacokinetic (PK/PD) experiment for which robenacoxib was administered at 2 mg/kg subcutaneously (SC). The objective of the study was to assess robenacoxib pharmacodynamic parameters by correlating concentration-effect relationships with analgesic, anti-inflammatory and antipyretic activity. Blood samples were collected and clinical endpoints (body temperature, locomotion score, locomotion test, local skin temperature and paw withdrawal time) were assessed at multiple times from Day 0 to Day 4 after kaolin injection. The effective dose for lameness and locomotion were determined to be 1.5 and 3 mg/kg respectively, after

SC administration of robenacoxib in the cat. Using a PK/PD simulation approach with the pharmacodynamic parameters obtained in this study and PK parameters calculated from oral pharmacokinetic data from two other studies, it was predicted that robenacoxib would provide good anti-inflammatory, antipyretic and analgesic activity after oral administration of 1 mg/kg in the cat.

The above studies indicated that a dose of 1 mg/kg administered orally once daily was an appropriate dose for further investigation. To confirm these results, a pilot study was conducted in client-owned animals to evaluate the effectiveness of robenacoxib tablets (final formulation) at a dose of 1 mg/kg administered once daily for the control of postoperative pain and inflammation associated with an onychectomy (forelimbs only) and ovariohysterectomy (OVH) or castration. The study was a masked, negative controlled, multi-center field study in which 24 cats were enrolled in the two groups (12 cats per treatment group). Each cat received either robenacoxib or the negative control approximately 30 minutes prior to surgery or at the same time the pre-anesthetic agents were administered and then daily for two days post-surgery. Animals were evaluated post-surgically at predetermined times to assess the overall response to treatment and to monitor their condition. Effectiveness variables included rescue therapy due to pain, overall pain, pain on palpation (orthopedic pain and OVH or castration incision site), posture, behavior and sedation. There were fewer cases needing rescue therapy in the robenacoxib group (3/12) compared to the negative control group (7/12). The difference was not statistically significant, presumably due to the low number of cats enrolled in the study. Overall pain, pain on palpation (orthopedic pain, and OVH or castration incision site), posture and behavior showed a reduction in mean overall values in favor of the robenacoxib group when compared to the negative control group. In this study, robenacoxib was well tolerated when used to control postoperative pain and inflammation associated with ovariohysterectomy or castration, and onychectomy. The results from this study indicated that the dose of 1 mg/kg should be effective for controlling postoperative pain and inflammation associated with an onychectomy and ovariohysterectomy or castration.

B. Substantial Evidence:

The effectiveness of ONSIOR tablets for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy (OVH) and castration was evaluated in cats presented for reproductive sterilization and forelimb onychectomy procedures. The study was conducted at twelve (12) veterinary clinics throughout various geographic regions within the U.S. Results of the study demonstrate that ONSIOR tablets are well-tolerated and effective when administered at a dose of 1 mg/kg of body weight once daily for a maximum of 3 days.

1. **Type of Study**: Field study

a. Title: Field effectiveness and safety of ONSIOR (tablet) for the control of postoperative pain and inflammation associated with ovariohysterectomy, castration and onychectomy in cats, (NAH-07-0001)

b. Investigators(s):

Dr. Deborah Edwards-Pettey Largo, FL	Dr. Sam Geller Quakertown, PA
Dr. Mary Gray Lafayette, IN	Dr. Amy Jessup Winston-Salem, NC
Dr. Joe Kinnarney Reidsville, NC	Dr. Kristi Rowland Lawrence, KS
Dr. Eddie Robinson Columbia, SC	Dr. Roger Sifferman Springfield, MO
Dr. Tammy Sadek Kentwood, MI	Dr. Phillip VanVranken Battle Creek, MI
Dr. Susan Streeter Oklahoma City, OK	Dr. Emily Walker Albuquerque, NM

c. Study Design: This was a masked, randomized, multi-center field study comparing ONSIOR tablets to a vehicle control (placebo).

1) Objective: The objective of the study was to demonstrate the effectiveness and field safety of ONSIOR tablets, at a dose of 1 mg/kg of body weight, for the control of postoperative pain and inflammation associated with reproductive sterilization performed in conjunction with an onychectomy (forelimbs only) in cats. As part of the pre-operative anesthetic protocol, all study participants received butorphanol tartrate and a forelimb metacarpal four-point ring block. In addition to the pre-operative therapy, treated animals received ONSIOR tablets as a pre-operative treatment and continued to receive it once daily for two additional treatments. Control animals received a placebo (vehicle control) at the same time points.

2) Study Animals: There were two hundred and forty-nine (110 males and 139 females) healthy, intact cats of various breeds, between 6 months and 13 years of age and weighing between 2.5 and 7.4 kg. The majority of cats were young. Of the 167 cats treated with robenacoxib, 161 (96%) were $\leq$ 4 years of age. Of the 167 cats treated with robenacoxib, 114 (68%) of these cats were 6 months to 1 year of age.

3) Treatment Groups: The animals were randomized into two treatment groups in a 2:1 ratio of ONSIOR tablet and vehicle control (placebo), respectively.

Body weight (kg)	6 mg ONSIOR (robenacoxib) Tablet	Placebo (vehicle control)
2.5 to 6	1 whole tablet once daily	1 whole tablet once daily
6.1 to 12	2 whole tablets once daily	2 whole tablets once daily

All cats received butorphanol subcutaneously as a pre-anesthetic medication and a metacarpal four-point ring block. Robenacoxib or placebo was administered approximately 30 minutes prior to surgery at the time of administration of pre-anesthetic medication.

Surgical procedures – All cats were adequately hydrated prior to and during surgery. Ovariohysterectomy was performed by a midline incision. Castrations were performed via the standard scrotal approach.

Onychectomy: Three types of procedures could be used to declaw the front paws. These included surgical scalpel, laser, and guillotine nail trimmers.

4) Drug Administration: The robenacoxib group received the final market formulation of ONSIOR tablets as 6 mg, non-scored tablets. The control group received placebo tablets (vehicle) identical in appearance. Robenacoxib or placebo was administered approximately 30 minutes prior to surgery at the time of administration of pre-anesthetic medication.

5) Measurements and Observations:

A clinical examination was conducted prior to surgery and at study exit. Assessments for pain were performed prior to surgery (following a minimum two hour acclimation) and at various time points on Day 0 (day of surgery), Day 1 (day after surgery) and Day 2 (day of discharge from hospital). Assessments included the need for rescue pain medication, posture, behavior (viewed from a distance and following social interaction), pain elicited on palpation (paws and incision site) and overall pain control. Hematology, serum chemistry and urine samples were obtained prior to study and at exit. In addition, all owners received a follow-up phone call 3-7 days post-study.

Scheduled evaluations and determination of the need for rescue pain medication were conducted at 0 minutes (extubation), 30

min, 1 hr, 3 hrs, 5 hrs, 8 hrs, 24 hrs, 28 hrs, 32 hrs, 48 hrs, and 52 hrs following surgery. Although these were the scheduled evaluation timepoints, rescue pain medication could be given any time at the veterinarian's discretion.

Pain Assessments: Cats were evaluated at baseline and at the pre-determined intervals postoperatively to assess overall response to treatment and to monitor the condition of the cats. At any time, if an animal was determined to be in discomfort, rescue pain medication could be administered. Cats receiving postoperative rescue pain treatment were considered treatment failures and withdrawn from the study. However, all cats continued to be monitored for a minimum of 24 hours post-intervention and all observations were recorded.

Posture: This variable assessed the cat's overall mobility in the cage, standing or resting, and any preferential or unequal weight distribution of the limbs, hunched or retracted posture, position of the head, and any forelimb shifting. The investigator assessed posture as one of the following:

1. Normal
2. Mildly abnormal (ambulates with slightly noticeable weight shifting behavior)
3. Moderately abnormal (Able to ambulate. Noticeable weight shifting behavior but still places affected limbs);
4. Severely abnormal (barely or unable to ambulate. Significant weight shifts or non-weight bearing behavior.)

Behavior: This variable assessed the cat's overall comfort, response to social interaction with the investigator or hospital staff, level of aggression, level of vocalization, and ease of handling as viewed from a distance and following social interaction. The investigator assessed behavior from a distance and following social interaction.

The investigator assessed *Behavior from a distance* as one of the following:

1. Appears comfortable
2. Questionable comfort
3. Distressed cat

The investigator assessed *Behavior following social interaction* as one of the following:

1. Normal

2. Mildly abnormal (slight reduction in level of social behavior but does not overtly object to examination or palpation);
3. Moderately abnormal (May try to avoid examination or palpation. May attempt to bite when affected areas are examined)
4. Severely abnormal (Refuses to be examined and may display aggression without provocation).

Pain elicited on palpation: This variable assessed the cat's level of response to a gradual increase in pressure applied to areas adjacent to the surgical sites. The endpoint of this assessment was the amount of pressure that elicited any level of pain response from the cat (e.g. withdrawal of paw, discomfort or vocalization).

Assessing the paws
Prior to surgery, the paw to be evaluated was determined and the same paw was assessed throughout the study.

The amount of pressure was measured via a palpometer, a pressure-sensing device. Based on the audio feedback, the investigator assessed this variable as one of the following:

1. 5 beeps (greatest recorded pressure) of pressure — equals 800 gf/cm^2
2. 4 beeps — equals 600 gf/cm^2
3. 3 beeps — equals 450 gf/cm^2
4. 2 beeps — equals 300 gf/cm^2
5. 1 beep (lightest recorded pressure) — equals 200 gf/cm^2

Assessing the soft tissue incision sites
The investigator was instructed not to use the palpometer or palpate directly over the incision site. An area immediately adjacent to the incision site was located and slowly digital pressure was applied. The area could be assessed several times and the veterinarian noted the severity of the cat's reaction in response to pressure. Applied pressure was stopped once the cat gave any indication of discomfort.

Based on a subjective evaluation, the investigator assessed this variable by indicating the cat responded to one of the following:

1. Significant pressure (response to a level of pressure that visually distorts the skin of the surgical area and was to a level that was nearly equivalent to what could be applied in a cat that had not undergone surgery).

2. Moderate pressure (response to a level of pressure that visually distorts the skin of the surgical area but does not approach the level of what could be normally accomplished had the cat not had surgery).
3. Slight pressure (response to any level of physical contact to the surgical area/field).

Overall pain control: This variable was a subjective assessment of the examiner's overall impression of pain control based on their assessment of posture, behavior and pain on palpation. The investigator assessed this variable as one of the following:

1. Well controlled (cat is clearly comfortable);
2. Moderately controlled (cat is generally comfortable with only slight indications of discomfort);
3. Poorly controlled (cat is clearly uncomfortable with overt signs of pain).

For each cat rescued due to poor pain control, investigators marked descriptors/reasons for intervention. Investigators were instructed to check all that applied from the following list.

- Difficult or violent post-anesthetic recovery. The patient may be thrashing violently in such a manner that may threaten their safety. Depending on the pre-anesthetic cocktail used, some post-anesthetic dysphoria may be encountered so clinical judgment should be used when determining the origin of such a recovery.
- Patient's posture is reflective of a purposeful avoidance of painful stimulus. The patient may exhibit purposeful forelimb shifting behavior or may be limping in order to alleviate pain caused by weight bearing. Care must be taken when such a behavior is exhibited in cats that have bandaged forelimbs.
- Patient has a hunched posture or any other positions where there is an obvious intent to avoid or move away from painful stimulus or surgical sites.
- Patient appears agitated or cannot find a comfortable position within the cage.
- Patient has poor or unkept appearance that may be reflective of poor grooming behaviors.
- Patient exhibits trembling or shaking that is not part of the dysphoria associated with the immediate anesthetic recovery and may be indicative of painful stimulus.
- Patient exhibits moderate to severe chewing, licking or biting of the surgical sites.
- Patient vocalizes in response to discomfort or pain.

- Patient demonstrates little or no social response to pain assessor or caregiver, prefers to be alone, and has little to no desire for social interaction.
- Patient demonstrates aggression or other defensive/guarding behaviors that are reflective of any discomfort associated with the surgical sites.
- Patient has moderate to severe tenderness of the surgical sites.
- Patient has moderate to severe tachycardia or tachypnea.
- Patient has dilated pupils.
- Other:

6) Statistical Methods: Summary tables (number of observations, means and standard deviations or median and frequency counts, and minimum and maximum values) were presented for all variables.

Effectiveness Variable

Animals that received rescue pain medication or were removed due to adverse events were considered treatment failures. The effectiveness variable was treatment success or failure. The pivotal test for effectiveness compared treatment success rates in the ONSIOR tablet group to the placebo group. A generalized linear mixed model (using GLIMMIX in SAS) was utilized, assuming a binomial distribution and a logit link function. The statistical model included 'Treatment' as a fixed effect and 'Site' and 'Site x Treatment' as random effects.

Individual Variables

The above noted individual variables of posture, behavior (viewed from a distance and following social interaction), pain elicited on palpation (paws and incision site) and overall pain control were assessed. Data from the day of surgery (extubation to hour 8), with Last Observation Carried Forward (LOCF) utilized on any animal that required rescue therapy on the day of surgery, was analyzed using generalized linear mixed models. The covariance was modeled using the AR(1) structure and the Kenward-Rogers adjustment was used to compute the denominator degrees of freedom for the test of the fixed effect.

d. Results:

Effectiveness was evaluated in 244 cats and field safety was evaluated in 249 cats. A statistically significant difference (p-value = 0.0476) in the

proportion of treatment successes in the ONSIOR tablets treatment group compared to the placebo control group was observed (Table 1).

Table 1. Results of the effectiveness analysis.

Treatment Group	N	Treatment Outcome (%)		P-value[a]
		Success	Failure	
ONSIOR	164	137 (83.5%)	27 (16.5%)	0.0476
Placebo	80	43 (53.8%)	37 (46.2%)	

[a] Treatment contrast based on generalized linear mixed model with logit link, using 'Treatment' as a fixed effect and 'Site' and 'Site x Treatment' as random effects.

Twenty-seven out of 164 robenacoxib cases (16.5%) and 37 out of 80 placebo cases (46.2%) were treatment failures. Of the 64 treatment failures, 49 cases (76.5% of the failures) were rescued/withdrawn by 24 hours post-surgery. Fourteen of the failures were rescued/withdrawn between 24 and 48 hours post-surgery (22% of failures). The remaining 1 case (1.5 %) was withdrawn after 48 hours post-surgery.

The most common descriptors checked by investigators for rescue were tenderness of surgical sites, aggressive/guarding behavior, vocalizing, and agitated, purposeful avoidance of painful stimulus, hunched position, trembling/shaking, little or no social response, and tachycardia/tachypnea.

For the individual variables, the analysis showed that for OVH or castration incision site pain, there were statistically significant ($P<0.05$) differences in incision site pain scores at assessment times 5 and 8 hours, indicating less pain in the ONSIOR group; and, in social behavior scores and posture scores at times 3, 5, and 8 hours, indicating less pain in the ONSIOR group. The statistical analysis did not converge for distance behavior score, overall pain control, and paw assessment pain score so no further comparisons were performed for these variables.

Body weight change was similar between both groups. No clinically significant difference existed between the ONSIOR tablets and the placebo group for hematology, serum chemistry or urinalysis results. Concurrent medications used during the field study with ONSIOR tablets included antiparasiticides, anesthetics, pre-anesthetic medications, and antibiotics.

e. Adverse Reactions: The most commonly reported adverse reactions were surgical site bleeding, infected surgery sites, lethargy and inappetance. The adverse reactions and number of cats experiencing each are summarized in Table 2. Some cats experienced more than one adverse reaction during the study.

Table 2. Adverse reactions reported in the field study.

Adverse Reaction*	ONSIOR 6 mg tablets N = 167	Placebo (vehicle tablets minus robenacoxib) N = 82
Inappetance, weight loss	4	2
Incision site bleeding	7	1
Incision site infection	6	2
Decreased activity, lethargy, hiding	4	1
Cystitis/hematuria	3	0
Hair loss, excoriation, bruising	2	0
Vomiting	4	1
Bloody stool, diarrhea	3	1
Respiratory, cardiac arrest	1	0
Incoordination, weakness	1	1
Death	0	1

*Cats may have experienced more than one type or occurrence of an event during the study.

f. Conclusion(s): Administration of ONSIOR tablets at a dose of 0.45 mg/lb (1 mg/kg) once daily for up to three days, with the first dose administered approximately 30 minutes prior to surgery, was effective and well-tolerated for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats.

III. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study of Robenacoxib Tablets in Cats:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Jennifer Bassett, BS
Ricerca Biosciences, LLC
Concord, OH

3. General Design:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets following daily oral administration over a 21 day period at 24 mg/kg/day (10X the maximum exposure).

b. Test Animals: Eight month old, healthy male and female domestic shorthair (DSH) cats were used in the study (4/sex/group)

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation, 6 mg robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Treatment Groups for the Drug Tolerance Study

Group	Dose	Number and Sex of Animals
1	0, empty gelatin capsules	4M, 4F
2	24 mg/kg/day	4M, 4F

g. Test duration: Twenty-one days

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical and neurologic examinations, body temperature, ophthalmic exams, coagulation and buccal mucosal bleeding times (BMBT), hematology and clinical chemistries, urinalyses, organ weights, and gross pathology and histopathology.

4. **Results**: All cats survived to termination of the study.

a. Adverse reactions included vomiting and decreased activity. Two cats in the 10X group exhibited abnormal rear limb neurologic function. One of these cats also exhibited a head tilt and nystagmus at the end of the study. Mean food consumption was less in the 10X group.

Food Consumption Mean Values:

	Pre (g)	**Week 1** (g)	**Week 2** (g)	**Week 3** (g)
Control	103.38	110.14	103.43	93.17
10X	101.56	90.91	88.48	83.98

b. Hematology and clinical chemistry evaluations showed a decrease in the mean calcium value in the 10X group compared to the controls, and mean cholesterol was higher in the 10X group compared to the controls. The mean potassium value was higher in the 10X group compared to the controls. All mean values remained within the reference range used for this study. The post-study pooled, urine specific gravity in the 10X group was lower compared to the control group; and the pooled urine volume was comparably higher in the 10X group compared to the controls.

d. Pathology findings and organ weights: The mean kidney weights were lower in the 10X group compared to the control group; and the mean thymus weights were also lower in the 10X group compared to the controls. There were some changes in pooled brain, heart, and spleen weights in the 10X group compared to controls. Two cats in the 10X group had either unilateral or bilateral extensive, chronic interstitial nephritis. There was a focal cecal/large intestinal erosion in one 10X cat. One 10X cat and one control cat had periportal, multifocal necrosis in one lobe of the liver. There were four 10X cats and 2 control cats with focal, extensive, unilateral or bilateral, renal tubular degeneration.

5. **Conclusions**: Under the conditions of this study, cats administered 24 mg/kg/day of robenacoxib remained clinically healthy throughout the 21 day duration, except for 2 cats in the 10X group with neurologic signs.

B. Target Animal Safety (TAS) Study of Robenacoxib Tablets Administered Daily to cats for Six Months

1. **Type of Study**: Laboratory safety study (GLP), 1X, 3X, and 5X TAS study

2. **Study Director**: Zac Lloyd, B.S.
MPI Research, Inc.
Mattawan, MI

3. **General Design**:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets, when orally administered, once daily to DSH, adult cats at 1X, 3X, and 5X the maximum exposure of 2.4 mg/kg for 6 months compared to placebo (the actual mg/kg dose received depended upon the cat's weight due to the inherent dose band of the non-scored, one-size, 6 mg tablet).

b. Test Animals: There were 3 treatment groups and 1 control group; 4/sex/group. The study used healthy, 8 month old DSH cats ranging in weight from 1.97 – 5.15 kg on the first day of dosing.

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation, 6 mg robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Treatment Groups for the 6 month TAS Study

Group	Dose	Number and Sex of Animals
1	0, empty gelatin capsules	4M, 4F
2	1X, 2. 4 mg/kg	4M, 4F
3	3X, 7.2 mg/kg	4M, 4F
4	5X, 12.0 mg/kg	4M, 4F

g. Test duration: Six months

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical and neurologic examinations, body temperature, fecal exams, ophthalmic exams, coagulation and buccal mucosal bleeding times (BMBT), hematology and clinical chemistries, urinalyses, electrocardiography, organ weights, and gross pathology and histopathology. Additionally, blood samples were collected for periodic pharmacokinetic analysis.

4. **Results**: All cats survived to termination of the study.

a. Abnormal clinical findings included one 5X cat that had clonic seizures on Day 115 and ataxia on Day 175. Another cat in the 5X group had skin cold to the touch on Day 106. One cat in the 1X group experienced urethral obstruction and feline lower urinary tract disease (FLUTD). Vomiting, decreased activity, injected sclera, and soft stools were the most common adverse reactions observed in the treated groups. Soft stools and injected sclera were also observed in the control group.

b. Pharmacokinetics: There was no obvious accumulation in C_{max} or AUC between Days 1, 31 and 171, and there was no apparent difference in parameters between males and females. The following parameters were

calculated for the 1X dosage: T_{max} was 0.5 h (median), the dose-normalized mean C_{max} was 668 ng/mL and the dose-normalized mean area under the curve (AUC (0-inf)) was 902 h*ng/mL. Similarly, the following parameters were calculated for the 3X dosage: T_{max} was 0.5 h (median), the dose-normalized mean C_{max} was 1019 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1394 h*ng/mL. For the 5X dosage the following parameters were calculated: T_{max} was 1.0 h (median), the dose-normalized mean C_{max} was 1198 ng/mL and the dose-normalized mean area under the curve (AUC(0-inf)) was 1884 h*ng/mL. A post hoc analysis of PK parameters revealed that dose normalized C_{max} and AUC were greater than dose proportional.

c. Body Weight: Significant mean body weight differences ($p \leq 0.0587$) were observed between the control group and all treated groups (lower than controls). These lower body weights (compared to the control group) were statistically significant for the 3X group from Day 35 – Day 182 ($p \leq 0.0587$) and statistically significant for the 1X and 5X groups from Day 49 – Day 182 ($p \leq 0.0487$).

d. Echocardiography: There was a clear dose-related and possible time-related increase in the QTc interval at Day 41 and Day 175. It is unknown if the increased QTc interval suggests an elevated risk of cardiac arrhythmias or Torsades de Pointe in cats.

   The control cats showed no increase in QTc intervals. In the 1X group, 1 cat showed an increase in QTc between 30 – 60 msec; and 13 cats showed interval increases of < 30 msec (7 cats on Day 41 and 6 cats on Day 175).

   In the 3X group, 4 cats showed an increase in QTc interval between 30 – 60 msec (1 cat on Day 41 and 3 cats on Day 175) and 9 cats showed increases of less than 30 msec (6 cats on Day 41 and 3 cats on Day 175).

   In the 5X group, there were 3 QTc interval increases > 60 msec (2 cats on Day 41 and 1 cat on Day 174); 3 increases between 30 – 60 msec (1 cat on Day 41 and 2 cats on Day 175), and 6 increases < 30 msec (4 on Day 41 and 2 on Day 175).

   No treatment effect was noted for heart rate, PR or RR intervals, or QRS duration.

e. Hematology and clinical chemistry evaluations: One 5X cat with decreased kidney weight and size also had transient increases in BUN and creatinine (BUN 44 mg/dL and creatinine 2.4 mg/dL on Day 90). This cat had bilateral renal tubular degeneration/regeneration with chronic inflammation. There were transient increases in aspartate aminotransferase (AST), amylase, and

alanine aminotransferase (ALT) in the 3X and 5X cats from Day 30 – Day 183. Compared to controls, there was a statistically significant difference in mean amylase in the 3X and 5X groups ($p \leq 0.0168$). The mean GGT values in the 1X and 3X groups on Day 183 were 40 IU/L and 50 IU/L higher than the Day 149 values, respectively.

f. Pathology findings and organ weights: The mean kidney weights were lower in all robenacoxib-treated groups compared to the control group. There were test article-related histopathology changes noted in the kidneys of two 1X cats and two 5X cats; the two 1X cats and one 5X cat had moderate, tubular degeneration/regeneration of greater severity than seen in any control cats. There was also the additional presence of inflammation, papillary necrosis and papillary mineralization in the kidneys of these treated cats. An additional 5X cat had minimal tubular degeneration/regeneration with minimal chronic inflammation.

   All treated cats had increased Kupffer cell pigmentation in the liver. In the treated cats, Kupffer cells were prominent with abundant brownish-tinged cytoplasm. There were no clinical signs noted, and the origin of the pigment is unknown.

   One 5X cat had focal, minimal degeneration/necrosis of the mucosal epithelial cells of the gastric fundus (peptic and parietal cells). In another safety study, a duodenal ulcer was also noted after 28 days in a cat administered 10 mg/kg robenacoxib per day.

5. **Conclusions**: All cats survived the 6 month study. Test article effects were noted on body weight, food consumption, QTc interval, and kidney and liver pathology. One treated cat had seizures and ataxia. An adequate safety margin was demonstrated for ONSIOR tablets when administered under the conditions of this study to support the use of the tablets for the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration in cats for a maximum of 3 days.

C. Target Animal Safety Study of Robenacoxib 6 mg Tablets Administered Orally, Twice Daily to Cats for 42 Days

1. **Type of Study**: Laboratory safety study (GLP)

2. **Study Director**: Rolf Hotz, DVM
   Novartis Centre de Recherche Sante Animale SA
   Switzerland

3. **General Design**:

a. Purpose: The objective of this laboratory study was to evaluate the safety of robenacoxib tablets administered orally, twice daily to adult cats 2 mg/kg (0.8X), 6 mg/kg (2.5X), and 10 mg/kg (4X) for 42 days.

b. Test Animals: Thirty-two healthy, DSH cats, 7.5 to 8 month of age were included in the 4 treatment groups (4/sex/group).

c. Control: Empty gelatin capsules

d. Dosage form: Gelatin capsules containing final market formulation robenacoxib tablets

e. Route of administration: Oral administration with water used to facilitate swallowing

f. Dosages used:

Treatment Groups for the 42 Day TAS Study

Group	Dose	Number and Sex of Animals
1	0	4 M, 4 F
2	0.8X, 2 mg/kg BID	4 M, 4 F
3	2.5X, 6 mg/kg BID	4 M, 4 F
4	4X, 10 mg/kg BID	4 M, 4 F

g. Test duration: Forty-two days

h. Variables measured: The following variables were measured prior to study initiation, during, and/or at the end of the study – body weight, food and water consumption, clinical observations, physical examinations, hematology and clinical chemistries, urinalyses, organ weights, and gross pathology and histopathology.

4. Results: All cats survived to termination of the study.

a. Clinical pathology: There was a mild increase in creatinine in the 1X group and a transient increase in BUN in the 3X group.

b. Pathology findings: Thymus weights were lower in all treated groups (atrophic changes were noted). There was a decrease in the kidney weights in the 5X group compared to the controls.

c. Adverse reactions: Vomiting was the most common adverse reaction noted in the treated cats. Other adverse reactions reported in other supportive safety studies included vomiting, diarrhea and lacrimation.

6. **Conclusions**: An adequate safety margin was demonstrated for ONSIOR tablets when administered under the conditions of this 42 day study.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ONSIOR tablets:

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental ingestion by humans. **For use in cats only.**"

VI. AGENCY CONCLUSIONS:

A. Marketing Status:

B. Exclusivity:

C. Patent Information:

ONSIOR is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,291,523	September 18, 2018
6,310,099	August 25, 2018
7,115,662	August 25, 2018

VII. ATTACHMENTS:

Exhibit G – Cover Letter, Administrative NADA

NOVARTIS
ANIMAL HEALTH

Novartis Animal Health US, Inc.
3200 Northline Avenue
Suite 300
Greensboro, NC 27408

336-387-1000

January 13, 2011

Document Control Unit
HFV-199, Room N403
FDA Center for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855

Attn: Dr. Mary Allen
HFV-110, Room N303

Subject:	NADA 141-320: Onsior® (robenacoxib) tablets for cats: **Administrative Application**

Dear Dr. Allen:

Novartis Animal Health US, Inc. (NAHUS) hereby submits the administrative application for NADA 141-320, ONSIOR (robenacoxib) Tablets for cats. Three copies consisting of 1 volume each are enclosed for this submission. The ADUFA fee has been submitted and a copy of the cover sheet is included.

This submission contains all technical section approval letters for INAD 11-241, final facsimile labeling and the final Freedom of Information summary.

Please find included:

Item	Date/Reference	Attachment #
ADUFA Cover Sheet		
Technical Section Complete for Target Animal Efficacy	September 25, 2009 I-011241-P-0103-EF	A
Technical Section Complete for Environmental Impact: Categorical Exclusion	August 19, 2010 I-011241-Q-0115-OT	B
Technical Section Complete for Target Animal Safety	October 13, 2010 I-011241-P-0110-TS	C
Technical Section Complete for Chemistry, Manufacturing and Controls	November 15, 2010 I-011241-P-0109-MC	D
Final Freedom Of Information Summary	December 20, 2010 I-011241-Q-0119-OT	E
Technical Section Complete for Labeling and Approved Facsimile Labeling	December 23, 2010 I-011241-M-0117-LB	F
Technical Section Complete for All Other Information	December 23, 2010 I-011241-M-0116-AO	G

US Express Mail EB 907 723642 US

NOVARTIS

The patent information for the Green Book consists of the following (also included in the Freedom of Information):

ONSIOR is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,291,523	September 18, 2018
6,310,099	August 25, 2018
7,115,662	August 25, 2018

NAHUS commits to filing final printed labeling to the NADA.

In accordance with 21 CFR 25.33(d)(1), we claim categorical exclusion from the requirement for an environmental assessment. This request was granted by CVM on August 19, 2010.

If there are any additional questions regarding this submission, please feel free to contact me at 1-800-447-2391 ext. 1009. Thank you very much.

Sincerely,

Elizabeth D. Norton

Elizabeth D. Norton, D.V.M.
Senior Regulatory Affairs Manager

enclosures